BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

CAS - update on Claims 5, 9 & 12

09/ 773,374 Supplemental

Welcome to STN International! Enter x:x

LOGINID:ssspta1202txn

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2	Apr 08	"Ask CAS" for self-help around the clock
NEWS 3	Jun 03	New e-mail delivery for search results now available
NEWS 4	Aug 08	PHARMAMarketLetter(PHARMAML) - new on STN
NEWS 5	Aug 19	Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
NEWS 6	Aug 26	Sequence searching in REGISTRY enhanced
NEWS 7	Sep 03	JAPIO has been reloaded and enhanced
NEWS 8	Sep 16	Experimental properties added to the REGISTRY file
NEWS 9	Sep 16	CA Section Thesaurus available in CAPLUS and CA
NEWS 10	Oct 01	CASREACT Enriched with Reactions from 1907 to 1985
NEWS 11	Oct 24	BEILSTEIN adds new search fields
NEWS 12	Oct 24	Nutraceuticals International (NUTRACEUT) now available on STN
NEWS 13	Nov 18	DKILIT has been renamed APOLLIT
NEWS 14	Nov 25	More calculated properties added to REGISTRY
NEWS 15	Dec 04	CSA files on STN
NEWS 16	Dec 17	PCTFULL now covers WP/PCT Applications from 1978 to date
NEWS 17	Dec 17	TOXCENTER enhanced with additional content
NEWS 18	Dec 17	Adis Clinical Trials Insight now available on STN
NEWS 19	Jan 29	Simultaneous left and right truncation added to COMPENDEX, ENERGY, INSPEC
NEWS 20	Feb 13	CANCERLIT is no longer being updated
NEWS 21	Feb 24	METADEX enhancements
NEWS 22	Feb 24	PCTGEN now available on STN
NEWS 23	Feb 24	TEMA now available on STN
NEWS 24	Feb 26	NTIS now allows simultaneous left and right truncation
NEWS 25	Feb 26	PCTFULL now contains images
NEWS 26	Mar 04	SDI PACKAGE for monthly delivery of multifile SDI results
NEWS 27	Mar 19	APOLLIT offering free connect time in April 2003
NEWS 28	Mar 20	EVENTLINE will be removed from STN
NEWS 29	Mar 24	PATDPAFULL now available on STN
NEWS 30	Mar 24	Additional information for trade-named substances without structures available in REGISTRY
NEWS 31	Apr 11	Display formats in DGENE enhanced
NEWS 32	Apr 14	MEDLINE Reload
NEWS 33	Apr 17	Polymer searching in REGISTRY enhanced
NEWS 34	Apr 21	Indexing from 1947 to 1956 being added to records in CA/CAPLUS
NEWS 35	Apr 21	New current-awareness alert (SDI) frequency in WPIDS/WPINDEX/WPIX

NEWS EXPRESS	April 4 CURRENT WINDOWS VERSION IS V6.01a, CURRENT MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP), AND CURRENT DISCOVER FILE IS DATED 01 APRIL 2003
NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS INTER	General Internet Information
NEWS LOGIN	Welcome Banner and News Items
NEWS PHONE	Direct Dial and Telecommunication Network Access to STN
NEWS WWW	CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that

specific topic.

All use of STN is subject to the provisions of the STN Customer agreement. Please note that this agreement limits use to scientific research. Use for software development or design or implementation of commercial gateways or other similar uses is prohibited and may result in loss of user privileges and other penalties.

* * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 09:59:27 ON 24 APR 2003

=> file reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 09:59:52 ON 24 APR 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 23 APR 2003 HIGHEST RN 504385-01-7
DICTIONARY FILE UPDATES: 23 APR 2003 HIGHEST RN 504385-01-7

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

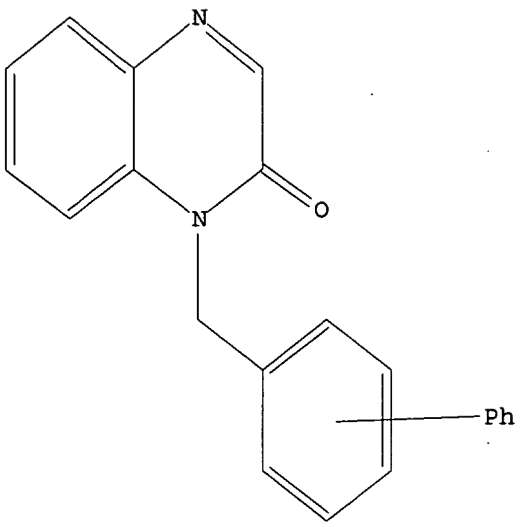
Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=>
Uploading 09773374c.str

L1 STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1 STR

09/ 773,374 Supplemental



Claim 9

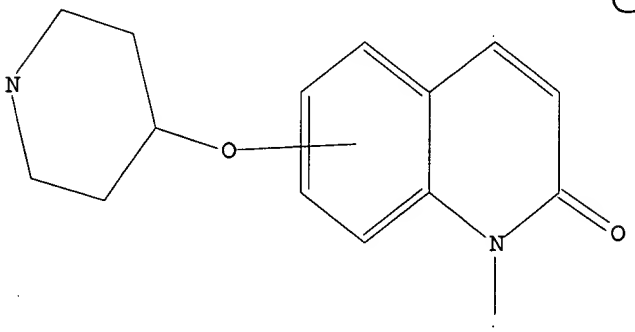
G1 C,O,S,N

Structure attributes must be viewed using STN Express query preparation.

=>
Uploading 09773734b.str

L2 STRUCTURE UPLOADED

=> d l2
L2 HAS NO ANSWERS
L2 STR



Claim 12

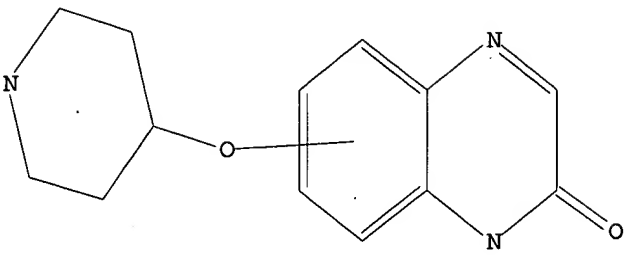
Structure attributes must be viewed using STN Express query preparation.

=>
Uploading 09773374a.str

L3 STRUCTURE UPLOADED

=> d l3
L3 HAS NO ANSWERS
L3 STR

09/ 773,374 Supplemental



Claim 5

Structure attributes must be viewed using STN Express query preparation.

```
=> s l1 ful
FULL SEARCH INITIATED 10:01:19 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -   4944 TO ITERATE

100.0% PROCESSED    4944 ITERATIONS                          1 ANSWERS
SEARCH TIME: 00.00.01

L4             1 SEA SSS FUL L1

=> s l2 ful
FULL SEARCH INITIATED 10:01:29 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -  25152 TO ITERATE

100.0% PROCESSED   25152 ITERATIONS                         19 ANSWERS
SEARCH TIME: 00.00.01

L5            19 SEA SSS FUL L2

=> s l3 ful
FULL SEARCH INITIATED 10:01:37 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -  13839 TO ITERATE

100.0% PROCESSED   13839 ITERATIONS                          0 ANSWERS
SEARCH TIME: 00.00.01

L6             0 SEA SSS FUL L3

=> file marpat
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                               444.85     445.06

FILE 'MARPAT' ENTERED AT 10:02:08 ON 24 APR 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2003 American Chemical Society (ACS)

FILE CONTENT: 1988-PRESENT (VOL 104 ISS 15-VOL 138 ISS16)(20030418/ED)

MOST RECENT CITATIONS FOR PATENTS FROM FIVE MAJOR ISSUING AGENCIES
(COVERAGE TO THESE DATES IS NOT COMPLETE):

US    6535373 18 MAR 2003
DE   10240388 20 MAR 2003
EP    1296401 26 MAR 2003
JP 2003092186 28 MAR 2003
WO 2003028051 04 APR 2003
```

09/ 773,374 Supplemental

Structure search limits have been raised. See HELP SLIMIT for the new, higher limits.

```
=> s l3
SAMPLE SEARCH INITIATED 10:02:20 FILE 'MARPAT'
SAMPLE SCREEN SEARCH COMPLETED -    284 TO ITERATE

100.0% PROCESSED     284 ITERATIONS                                1 ANSWERS
SEARCH TIME: 00.00.03

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:         4682 TO     6678
PROJECTED ANSWERS:               1 TO       80

L7             1 SEA SSS SAM L3

=> s l3 ful
FULL SEARCH INITIATED 10:02:28 FILE 'MARPAT'
FULL SCREEN SEARCH COMPLETED -   6200 TO ITERATE

100.0% PROCESSED    6200 ITERATIONS                                3 ANSWERS
SEARCH TIME: 00.00.17

L8             3 SEA SSS FUL L3

=> file caplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                     104.55     549.61

FILE 'CAPLUS' ENTERED AT 10:02:51 ON 24 APR 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)
```



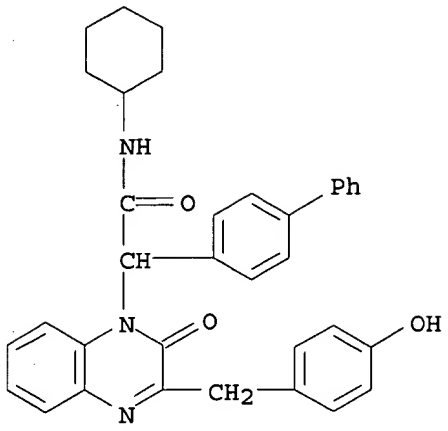
```
FILE COVERS 1907 - 24 Apr 2003  VOL 138 ISS 17
FILE LAST UPDATED: 23 Apr 2003  (20030423/ED)

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.


=> d his

     (FILE 'HOME' ENTERED AT 09:59:27 ON 24 APR 2003)

     FILE 'REGISTRY' ENTERED AT 09:59:52 ON 24 APR 2003
L1             STRUCTURE UPLOADED
L2             STRUCTURE UPLOADED
L3             STRUCTURE UPLOADED
```

09/ 773,374 Supplemental

```
L4             1 S L1 FUL
L5            19 S L2 FUL
L6             0 S L3 FUL

     FILE 'MARPAT' ENTERED AT 10:02:08 ON 24 APR 2003
L7             1 S L3
L8             3 S L3 FUL

     FILE 'CAPLUS' ENTERED AT 10:02:51 ON 24 APR 2003

=> s l4
L9             1 L4

=> d l9 1- ibib abs hitstr
YOU HAVE REQUESTED DATA FROM 1 ANSWERS - CONTINUE? Y/(N):y

L9   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:         2002:136805  CAPLUS
DOCUMENT NUMBER:          137:124760
TITLE:                    Two-step solution-phase synthesis of novel
                          quinoxalinones utilizing a UDC (Ugi/de-
                          Boc/cyclization) strategy
AUTHOR(S):                Nixey, Thomas; Tempest, Paul; Hulme, Christopher
CORPORATE SOURCE:         Department of Small Molecule Drug Discovery, AMGEN
                          Inc., Thousand Oaks, CA, 91320, USA
SOURCE:                   Tetrahedron Letters (2002), 43(9), 1637-1639
                          CODEN: TELEAY; ISSN: 0040-4039
PUBLISHER:                Elsevier Science Ltd.
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
OTHER SOURCE(S):          CASREACT 137:124760
AB   A novel soln.-phase synthesis of an array of biol. relevant quinoxalinones
     in a simple two-step procedure is revealed.  Transformations are carried
     out in excellent yield by condensation of mono-Boc protected
     ortho-phenylene di-amine, glyoxylic acids and supporting Ugi reagents.
     Subsequent acid treatment and evapn. affords quinoxalinones in good to
     excellent yields.  The BOC-protected component in this strategy was
     N-(2-aminophenyl)-2,2-dimethylpropanamide.  Glyoxylic acid derivs.
     included .alpha.-oxobenzeneacetic acid, .alpha.-oxo-1H-indole-3-acetic
     acid, 4-hydroxy-.alpha.-oxobenzenepropanoic acid.  Aldehydes included
     benzenepropanal, 3-hydroxybenzaldehyde, 6-methyl-2-pyridinecarboxaldehyde,
     2-formylcyclopropanecarboxylic acid Et ester, 2-methylpropanal,
     [1,1'-biphenyl]-4-carboxaldehyde.  Isocyanides included
     (isocyano)cyclohexane, 4-isocyano-1-(phenylmethyl)piperidine, etc.
     Example compds. thus prepd. included N-cyclohexyl-2-oxo-3-phenyl-.alpha.-
     (2-phenylethyl)-1(2H)-quinoxalineacetamide and N-cyclohexyl-.alpha.-(6-
     methyl-2-pyridinyl)-2-oxo-3-phenyl-1(2H)-quinoxalineacetamide.
IT   443890-05-9P
     RL: SPN (Synthetic preparation); PREP (Preparation)
        (two-step soln.-phase synthesis of 2-oxo-1(2H)-quinoxalineacetamides
        via Ugi reaction/deprotection/cyclization strategy)
RN   443890-05-9  CAPLUS
CN   1(2H)-Quinoxalineacetamide, .alpha.-[1,1'-biphenyl]-4-yl-N-cyclohexyl-3-
     [(4-hydroxyphenyl)methyl]-2-oxo- (9CI)  (CA INDEX NAME)
```

late

Related US cases all ABN



REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> s l5
L10 1 L5

=> d l10 1- ibib abs hitstr
YOU HAVE REQUESTED DATA FROM 1 ANSWERS - CONTINUE? Y/(N):y

L10 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:581872 CAPLUS
DOCUMENT NUMBER: 135:147430
TITLE: 2-[1H]-quinolone and 2-[1H]-quinoxalone inhibitors of factor Xa, pharmaceutical compositions, and therapeutic use
INVENTOR(S): Zhu, Bing-Yan; Scarborough, Robert
PATENT ASSIGNEE(S): Cor Therapeutics, Inc., USA
SOURCE: PCT Int. Appl., 66 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

applicant's pregrant version

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001057021	A2	20010809	WO 2001-US3176	20010201
WO 2001057021	A3	20020214		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002058657	A1	20020516	US 2001-773374	20010201
EP 1255741	A2	20021113	EP 2001-906827	20010201
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.:
US 2000-179389P P 20000201
US 2000-191722P P 20000324
WO 2001-US3176 W 20010201

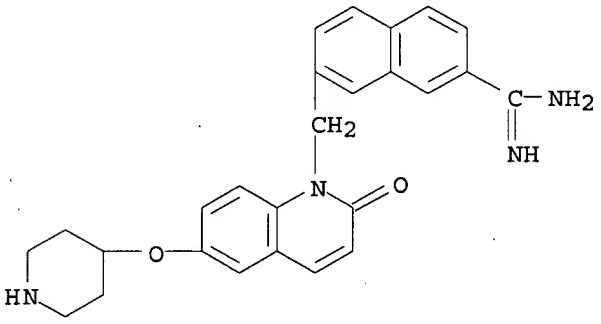
OTHER SOURCE(S): MARPAT 135:147430

AB The title compds. (Markush included), including their pharmaceutically acceptable isomers, salts, hydrates, solvates, and prodrug derivs., having activity against mammalian factor Xa, are described. Compns. contg. such compds. are also described. The compds. and compns. are useful in vitro or in vivo for preventing or treating conditions in mammals characterized by undesired thrombosis.

IT **353237-84-0 353237-85-1 353237-86-2**
353237-87-3 353237-88-4 353237-89-5
353237-90-8 353237-91-9 353237-92-0
353237-93-1 353237-94-2 353237-95-3
353237-96-4 353237-97-5 353237-98-6
353237-99-7 353238-00-3 353238-01-4
353238-02-5
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(quinolone and quinoxalone inhibitors of factor Xa, pharmaceutical compns., and therapeutic use)

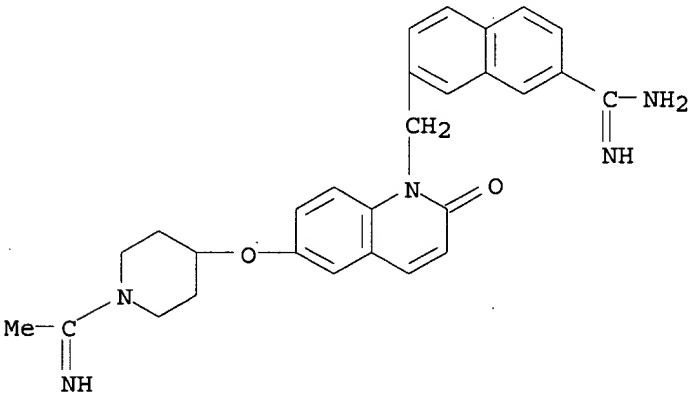
RN 353237-84-0 CAPLUS

CN 2-Naphthalenecarboximidamide, 7-[[2-oxo-6-(4-piperidinyloxy)-1(2H)-quinolinyl]methyl]- (9CI) (CA INDEX NAME)



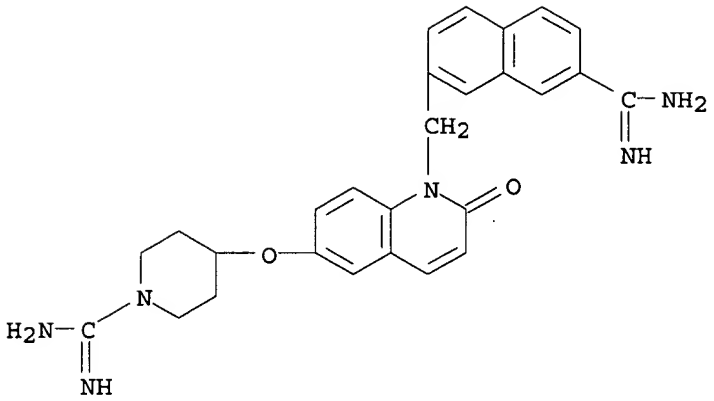
RN 353237-85-1 CAPLUS

CN 2-Naphthalenecarboximidamide, 7-[[6-[[1-(1-iminoethyl)-4-piperidinyl]oxy]-2-oxo-1(2H)-quinolinyl]methyl]- (9CI) (CA INDEX NAME)

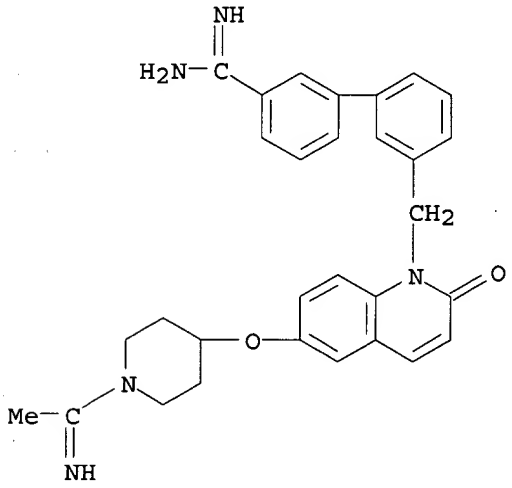


RN 353237-86-2 CAPLUS

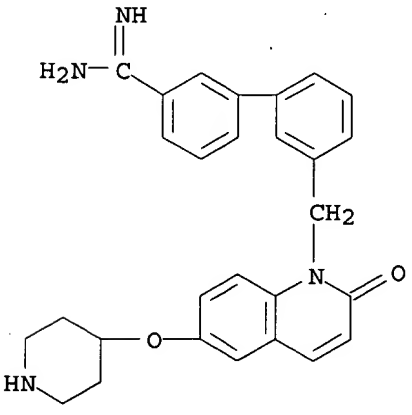
CN 1-Piperidinecarboximidamide, 4-[[1-[[7-(aminoiminomethyl)-2-naphthalenyl]methyl]-1,2-dihydro-2-oxo-6-quinolinyl]oxy]- (9CI) (CA INDEX NAME)



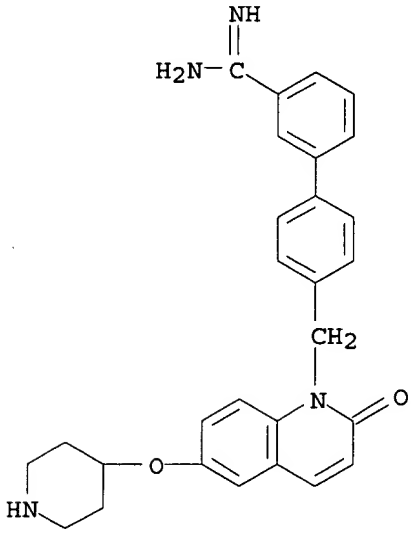
RN 353237-87-3 CAPLUS
CN [1,1'-Biphenyl]-3-carboximidamide, 3'-[[6-[[1-(1-iminoethyl)-4-piperidinyl]oxy]-2-oxo-1(2H)-quinolinyl]methyl]- (9CI) (CA INDEX NAME)



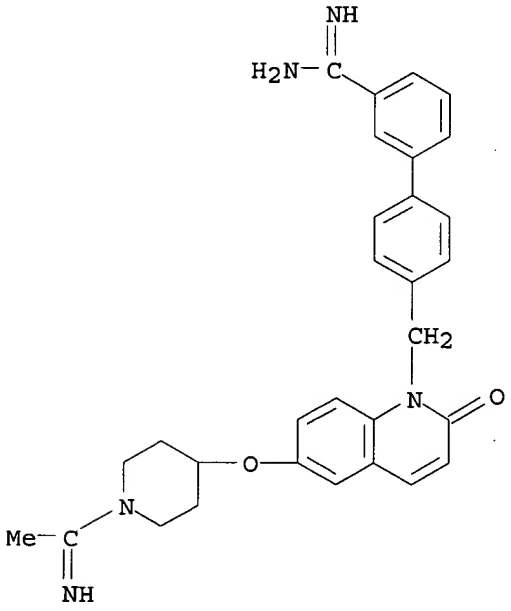
RN 353237-88-4 CAPLUS
CN [1,1'-Biphenyl]-3-carboximidamide, 3'-[[2-oxo-6-(4-piperidinyloxy)-1(2H)-quinolinyl]methyl]- (9CI) (CA INDEX NAME)



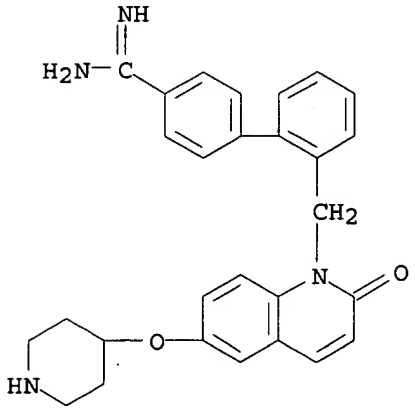
RN 353237-89-5 CAPLUS
CN [1,1'-Biphenyl]-3-carboximidamide, 4'-[[2-oxo-6-(4-piperidinyloxy)-1(2H)-quinolinyl]methyl]- (9CI) (CA INDEX NAME)



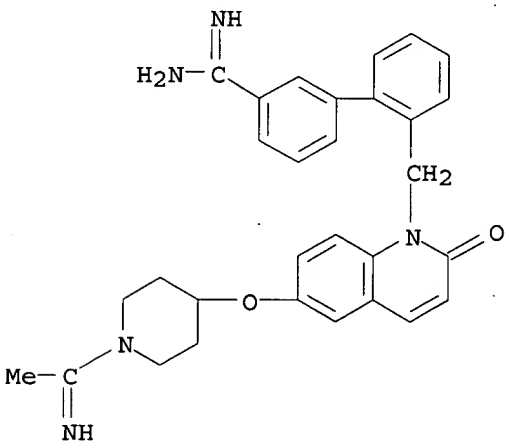
RN 353237-90-8 CAPLUS
CN [1,1'-Biphenyl]-3-carboximidamide, 4'-[[6-[[1-(1-iminoethyl)-4-piperidinyl]oxy]-2-oxo-1(2H)-quinolinyl]methyl]- (9CI) (CA INDEX NAME)



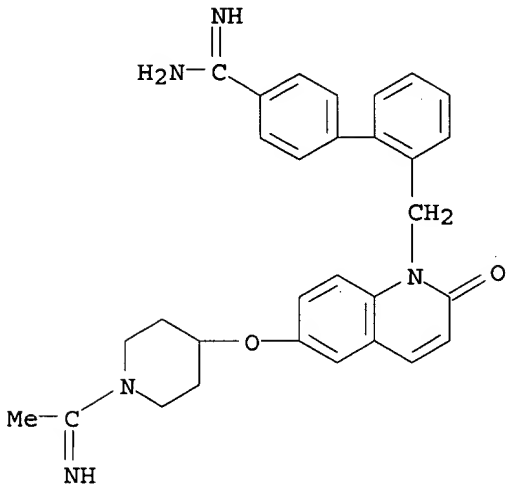
RN 353237-91-9 CAPLUS
CN [1,1'-Biphenyl]-4-carboximidamide, 2'-[[2-oxo-6-(4-piperidinyloxy)-1(2H)-quinolinyl]methyl]- (9CI) (CA INDEX NAME)



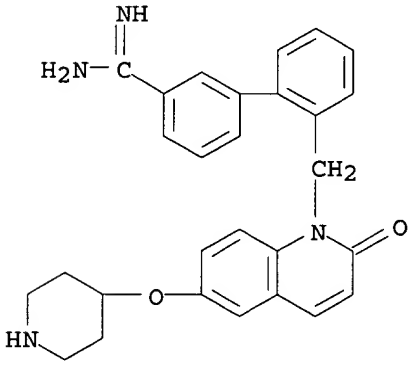
RN 353237-92-0 CAPLUS
CN [1,1'-Biphenyl]-3-carboximidamide, 2'-[[6-[[1-(1-iminoethyl)-4-piperidinyl]oxy]-2-oxo-1(2H)-quinolinyl]methyl]- (9CI) (CA INDEX NAME)



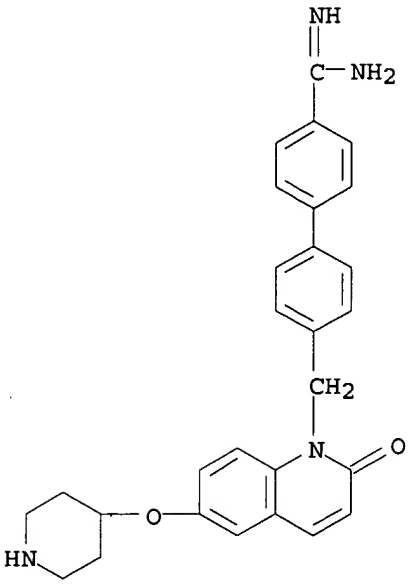
RN 353237-93-1 CAPLUS
CN [1,1'-Biphenyl]-4-carboximidamide, 2'-[[6-[[1-(1-iminoethyl)-4-piperidinyl]oxy]-2-oxo-1(2H)-quinolinyl]methyl]- (9CI) (CA INDEX NAME)



RN 353237-94-2 CAPLUS
CN [1,1'-Biphenyl]-3-carboximidamide, 2'-[[2-oxo-6-(4-piperidinyloxy)-1(2H)-quinolinyl]methyl]- (9CI) (CA INDEX NAME)

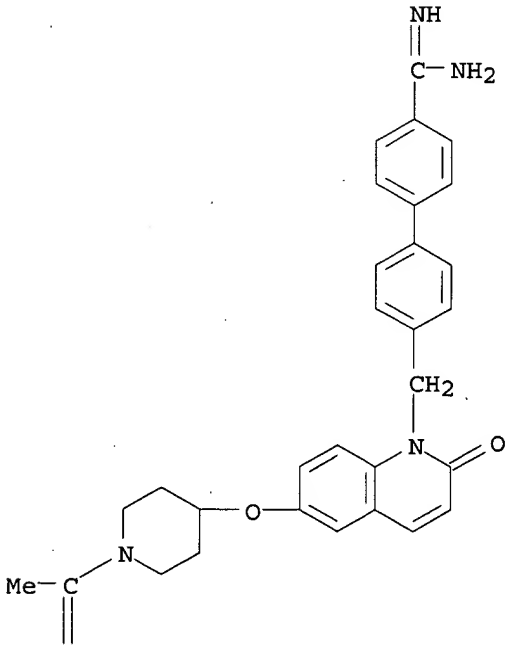


RN 353237-95-3 CAPLUS
CN [1,1'-Biphenyl]-4-carboximidamide, 4'-[[2-oxo-6-(4-piperidinyloxy)-1(2H)-quinolinyl]methyl]- (9CI) (CA INDEX NAME)



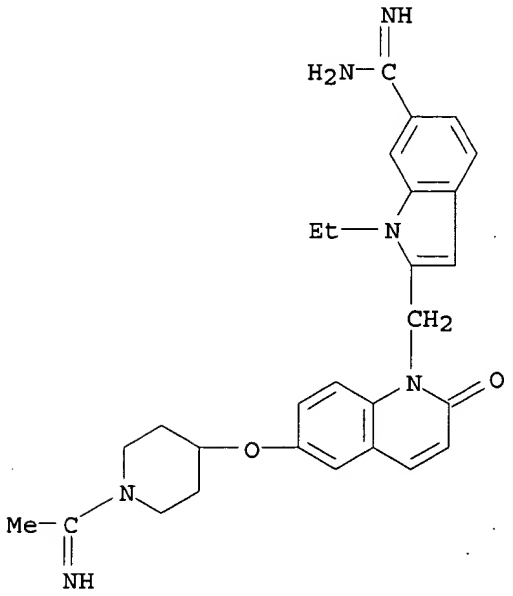
RN 353237-96-4 CAPLUS
CN [1,1'-Biphenyl]-4-carboximidamide, 4'-[[6-[[1-(1-iminoethyl)-4-piperidinyl]oxy]-2-oxo-1(2H)-quinolinyl]methyl]- (9CI) (CA INDEX NAME)

PAGE 1-A

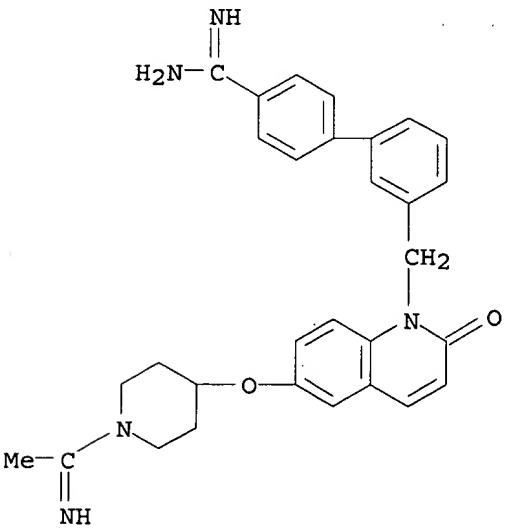


PAGE 2-A

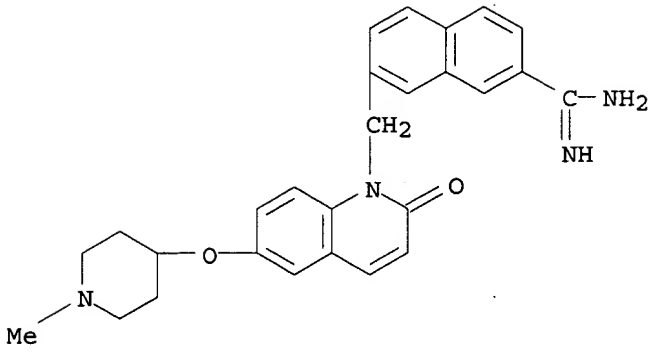
RN 353237-97-5 CAPLUS
CN 1H-Indole-6-carboximidamide, 1-ethyl-2-[[6-[[1-(1-iminoethyl)-4-piperidinyl]oxy]-2-oxo-1(2H)-quinolinyl]methyl]- (9CI) (CA INDEX NAME)



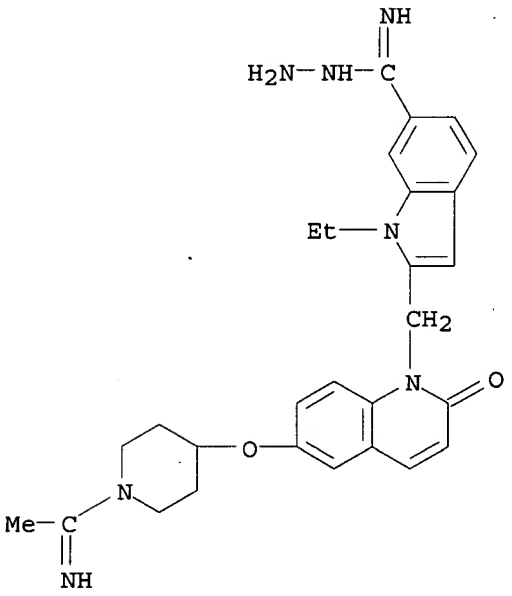
RN 353237-98-6 CAPLUS
CN [1,1'-Biphenyl]-4-carboximidamide, 3'-[[6-[[1-(1-iminoethyl)-4-piperidinyl]oxy]-2-oxo-1(2H)-quinolinyl]methyl]- (9CI) (CA INDEX NAME)



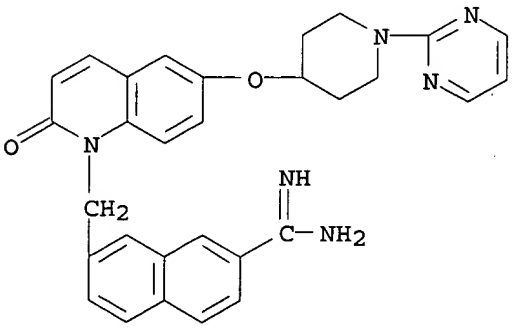
RN 353237-99-7 CAPLUS
CN 2-Naphthalenecarboximidamide, 7-[[6-[(1-methyl-4-piperidinyl)oxy]-2-oxo-1(2H)-quinolinyl]methyl]- (9CI) (CA INDEX NAME)



RN 353238-00-3 CAPLUS
CN 1H-Indole-6-carboximidic acid, 1-ethyl-2-[[6-[[1-(1-iminoethyl)-4-piperidinyl]oxy]-2-oxo-1(2H)-quinolinyl]methyl]-, hydrazide (9CI) (CA INDEX NAME)

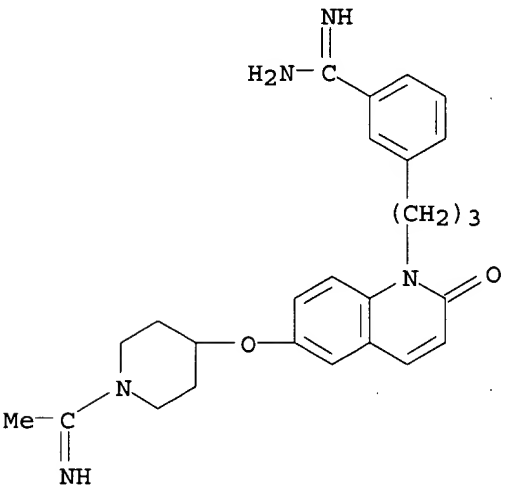


RN 353238-01-4 CAPLUS
CN 2-Naphthalenecarboximidamide, 7-[[2-oxo-6-[[1-(2-pyrimidinyl)-4-piperidinyl]oxy]-1(2H)-quinolinyl]methyl]- (9CI) (CA INDEX NAME)



09/ 773,374 Supplemental

RN 353238-02-5 CAPLUS
CN Benzenecarboximidamide, 3-[3-[6-[[1-(1-iminoethyl)-4-piperidinyl]oxy]-2-oxo-1(2H)-quinolinyl]propyl]- (9CI) (CA INDEX NAME)



=> s l8
L11 3 L8

=> d l11 1- ibib abs hitstr
YOU HAVE REQUESTED DATA FROM 3 ANSWERS - CONTINUE? Y/(N):y

L11 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:574925 CAPLUS
DOCUMENT NUMBER: **137:140442**
TITLE: Preparation of 1,5-diaryl-7-heterocyclyl(alkyl)-2-quinolinones as p38 protein kinase inhibitors
INVENTOR(S): Doherty, James B.; Stelmach, John E.; Chen, Meng-Hsin; Liu, Luping; Hunt, Julianne A.; Ruzek, Rowena D.; Goulet, Joung L.; Wisnoski, David D.; Natarajan, Swaminathan Ravi; Rupprecht, Kathleen M.; Bao, Jianming; Miao, Shouwu; Hong, Xingfang
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 440 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002058695	A1	20020801	WO 2001-US48676	20011214

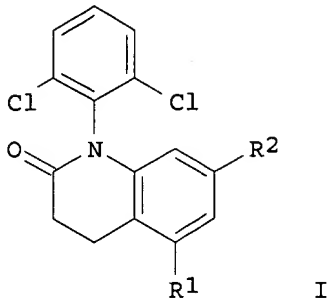
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-256822P P 20001220

60/256,822 ~~US6442880~~

09/ 773,374 Supplemental

OTHER SOURCE(S): MARPAT 137:140442
GI



I

AB Title compds. were prepd. Thus, 2,6-dibromo-4-methoxytoluene was converted in 5 steps to arylquinolinone I (R1 = Br, R2 = OMe) which was condensed with 2,4-F2C6H3B(OH)2 and the O-demethylated product converted in 4 steps to I (R1 = C6H3F2-2,4, R2 = 4-piperidinyl). Data for biol. activity of title compds. were given.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:581872 CAPLUS
DOCUMENT NUMBER: **135:147430**
TITLE: 2-[1H]-quinolone and 2-[1H]-quinoxalone inhibitors of factor Xa, pharmaceutical compositions, and therapeutic use
INVENTOR(S): Zhu, Bing-Yan; Scarborough, Robert
PATENT ASSIGNEE(S): Cor Therapeutics, Inc., USA
SOURCE: PCT Int. Appl., 66 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

applicants program version

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001057021	A2	20010809	WO 2001-US3176	20010201
WO 2001057021	A3	20020214		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002058657	A1	20020516	US 2001-773374	20010201
EP 1255741	A2	20021113	EP 2001-906827	20010201
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.: US 2000-179389P P 20000201
US 2000-191722P P 20000324
WO 2001-US3176 W 20010201

OTHER SOURCE(S): MARPAT 135:147430

AB The title compds. (Markush included), including their pharmaceutically acceptable isomers, salts, hydrates, solvates, and prodrug derivs., having activity against mammalian factor Xa, are described. Compns. contg. such compds. are also described. The compds. and compns. are useful in vitro or in vivo for preventing or treating conditions in mammals characterized by undesired thrombosis.

L11 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1999:487291 CAPLUS

DOCUMENT NUMBER: **131:116262**

TITLE: Preparation of novel benzene-fused heterocyclic derivatives as anticoagulant

INVENTOR(S): Hirayama, Fukushi; Koshio, Hiroyuki; Ishihara, Tsukasa; Kaizawa, Hiroyuki; Katayama, Naoko; Taniuchi, Yuta; Matsumoto, Yuzo

PATENT ASSIGNEE(S): Yamanouchi Pharmaceutical Co., Ltd., Japan

SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9937643	A1	19990729	WO 1999-JP276	19990125
W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9920746	A1	19990809	AU 1999-20746	19990125

PRIORITY APPLN. INFO.: JP 1998-12970 19980126
WO 1999-JP276 19990125

OTHER SOURCE(S): MARPAT 131:116262

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. [I; or salts thereof, R1 = Q1, Q2; A = -CH=CCH3-CH2-, -CH2-CH2-CH2-, -NH-CO-CH2-, -O-CH2-CH2-; Z = a bond, -CO-, -CO-O-, -SO2-; Y = lower alkylene, -NH-CO-, -CH2-NH-CO-, -NMe-CH2, -C(CO2Me)=CH-; R2 = hydrogen, lower alkyl, forming -(CH=CH)2-; R3 = H, C(:NH)CH3] are prepd. via cyclization and have anticoagulant effects based on inhibition of activated blood coagulation factor X, these compds. are useful as blood anticoagulants or preventives/remedies for diseases induced by thrombosis or embolism. The title compd. II was prepd.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d his

(FILE 'HOME' ENTERED AT 09:59:27 ON 24 APR 2003)

FILE 'REGISTRY' ENTERED AT 09:59:52 ON 24 APR 2003

09/ 773,374 Supplemental

```
L1                STRUCTURE UPLOADED
L2                STRUCTURE UPLOADED
L3                STRUCTURE UPLOADED
L4             1 S L1 FUL
L5            19 S L2 FUL
L6             0 S L3 FUL

      FILE 'MARPAT' ENTERED AT 10:02:08 ON 24 APR 2003
L7             1 S L3
L8             3 S L3 FUL

      FILE 'CAPLUS' ENTERED AT 10:02:51 ON 24 APR 2003
L9             1 S L4
L10            1 S L5
L11            3 S L8

=> log y
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                      ENTRY    SESSION
FULL ESTIMATED COST                                     17.99     567.60

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                      ENTRY    SESSION
CA SUBSCRIBER PRICE                                     -3.26      -3.26

STN INTERNATIONAL LOGOFF AT 10:05:15 ON 24 APR 2003
```

09/ 773,374

Welcome to STN International! Enter x:x

LOGINID:ssspta1202txn

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2	Jan 25	BLAST(R) searching in REGISTRY available in STN on the Web
NEWS 3	Jan 25	Searching with the P indicator for Preparations
NEWS 4	Jan 29	FSTA has been reloaded and moves to weekly updates
NEWS 5	Feb 01	DKILIT now produced by FIZ Karlsruhe and has a new update frequency
NEWS 6	Feb 19	Access via Tymnet and SprintNet Eliminated Effective 3/31/02
NEWS 7	Mar 08	Gene Names now available in BIOSIS
NEWS 8	Mar 22	TOXLIT no longer available
NEWS 9	Mar 22	TRCTHERMO no longer available
NEWS 10	Mar 28	US Provisional Priorities searched with P in CA/CAplus and USPATFULL
NEWS 11	Mar 28	LIPINSKI/CALC added for property searching in REGISTRY

NEWS EXPRESS	February 1 CURRENT WINDOWS VERSION IS V6.0d, CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP), AND CURRENT DISCOVER FILE IS DATED 05 FEBRUARY 2002
NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS INTER	General Internet Information
NEWS LOGIN	Welcome Banner and News Items
NEWS PHONE	Direct Dial and Telecommunication Network Access to STN
NEWS WWW	CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that specific topic.

* * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 14:07:50 ON 01 APR 2002

=> file reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 14:07:58 ON 01 APR 2002

STRUCTURE FILE UPDATES: 31 MAR 2002 HIGHEST RN 403640-18-6
DICTIONARY FILE UPDATES: 31 MAR 2002 HIGHEST RN 403640-18-6

TSCA INFORMATION NOW CURRENT THROUGH July 7, 2001

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Calculated physical property data is now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

The P indicator for Preparations was not generated for all of the CAS Registry Numbers that were added to the H/Z/CA/CAplus files between 12/27/01 and 1/23/02. Use of the P indicator in online and SDI searches during this period, either directly appended to a CAS Registry Number or by qualifying an L-number with /P, may have yielded incomplete results. As of 1/23/02, the situation has been resolved. Also, note that searches conducted using the PREP role indicator were not affected.

Customers running searches and/or SDIs in the H/Z/CA/CAplus files incorporating CAS Registry Numbers with the P indicator between 12/27/01 and 1/23/02, are encouraged to re-run these strategies. Contact the CAS Help Desk at 1-800-848-6533 in North America or 1-614-447-3698, worldwide, or send an e-mail to help@cas.org for further assistance or to receive a credit for any duplicate searches.

=>
Uploading 09773374.str

L1 STRUCTURE UPLOADED

=> s l1
SAMPLE SEARCH INITIATED 14:08:13 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 10602 TO ITERATE

  9.4% PROCESSED 1000 ITERATIONS 50 ANSWERS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 205880 TO 218200
PROJECTED ANSWERS: 12008 TO 15132

L2 50 SEA SSS SAM L1

=> s l1 ful
FULL SEARCH INITIATED 14:08:20 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 213498 TO ITERATE

100.0% PROCESSED 213498 ITERATIONS 12751 ANSWERS
SEARCH TIME: 00.00.07

L3 12751 SEA SSS FUL L1

=> file caplus
COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION
FULL ESTIMATED COST 140.66 140.87

FILE 'CAPLUS' ENTERED AT 14:08:56 ON 01 APR 2002

09/ 773,374

FILE COVERS 1907 - 1 Apr 2002 VOL 136 ISS 14
FILE LAST UPDATED: 30 Mar 2002 (20020330/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

CAS roles have been modified effective December 16, 2001. Please check your SDI profiles to see if they need to be revised. For information on CAS roles, enter HELP ROLES at an arrow prompt or use the CAS Roles thesaurus (/RL field) in this file.

The P indicator for Preparations was not generated for all of the CAS Registry Numbers that were added to the CAS files between 12/27/01 and 1/23/02. As of 1/23/02, the situation has been resolved. Searches and/or SDIs in the H/Z/CA/CAplus files incorporating CAS Registry Numbers with the P indicator executed between 12/27/01 and 1/23/02 may be incomplete. See the NEWS message on this topic for more information.

```
=> s l3
L4        2424 L3

=> s l4 and (thrombosis or thrombus or cardiac or angina or infarct?)
         14332 THROMBOSIS
          5983 THROMBUS
         87176 CARDIAC
          5776 ANGINA
         22874 INFARCT?
L5          61 L4 AND (THROMBOSIS OR THROMBUS OR CARDIAC OR ANGINA OR INFARCT?)

=> d l5 1- ibib abs fhitstr
YOU HAVE REQUESTED DATA FROM 61 ANSWERS - CONTINUE? Y/(N):y

L5   ANSWER 1 OF 61  CAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:         2001:762988  CAPLUS
DOCUMENT NUMBER:          135:331346
TITLE:                    Synthesis of benzoamide piperidine containing
                          compounds as substance P antagonists
INVENTOR(S):              Arnold, Eric Platt; Chappie, Thomas Allen; Huang,
                          Jianhua; Humphrey, John Michael; Nagel, Arthur Adam;
                          O'Neill, Brian Thomas; Sobolov-Jaynes, Susan Beth;
                          Vincent, Lawrence Albert
PATENT ASSIGNEE(S):       Pfizer Products Inc., USA
SOURCE:                   PCT Int. Appl., 209 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:
```

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001077100	A2	20011018	WO 2001-IB629	20010406

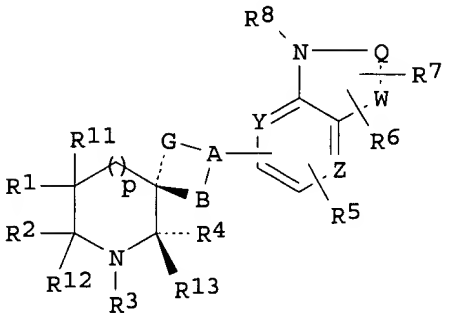
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

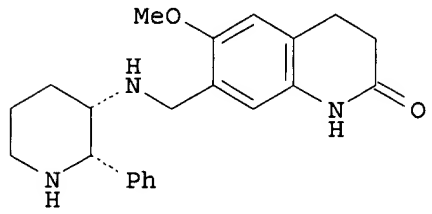
PRIORITY APPLN. INFO.: US 2000-195922P P 20000410
US 2000-212922P P 20000620

OTHER SOURCE(S): MARPAT 135:331346

GI



I



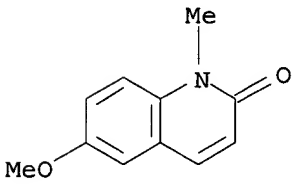
II

AB Title compds. I [Q = C:NH, C:CH2, C:S, C:O, SO, SO2; A = CH, CH2, C(alkyl), CH(alkyl), C(CF3), or CH(CF3) with the proviso that when B is present, A = CH, C(alkyl), or C(CF3); B = absent, CH2, or ethylene; Y, Z = N, CH, provided that both are not N; G = NH(CH2)q, S(CH2)q, O(CH2)q; q = 0-1 with the proviso that when q = 0, G = NH2, SH, OH; W = 1-3 carbon linking group, including spiro assemblies; p = 0-2; R3 = H, acyl, carboxy, Ph, heterocyclyl, alkyl, etc.; R1, R2, R11-13 = H, alkyl, etc., or R12-13 together with the carbon atoms to which they are attached form a 5- or 6-membered heterocyclic ring, etc.; R4 = Ph, pyridyl, thienyl, etc.; R5-8 = H, alkyl, S(O)1-2-alkyl, S(O)1-2-aryl, alkoxy, halo, Ph, etc.] were prepd. Approx. 100 synthetic examples and over 100 precursor prepns. were provided. For instance, 4-aminophenol was acylated with 3-chloropropionyl chloride (CH2Cl2, H2O, NaHCO3, room temp., 4 h) and the product treated with AlCl3 at 210.degree.C for 10 min effecting cyclization to the hydroxy quinolone intermediate. The intermediate was O-methylated (acetone, Me2SO4, K2CO3, room temp., 16 h) and formylated in the 7 position (CH2Cl2, AlCl3, Cl2CHOMe) to give 7-formyl-6-methoxy-1H-1,2,3,4-tetrahydroquinolin-2-one. Reductive alkylation of the quinolone with (2S,3S)-3-amino-2-phenylpiperidine (a. PhMe, 3.ANG. mol. sieves; b. dichloroethane,

NaHB(OAc)3, room temp., 16 h) yielded II. Compds. I are NK-1 receptor antagonists, i.e., substance P receptor antagonists. At least one stereoisomer of the example compds. had a binding affinity, as measured by Ki, of at least 600 nM. I are used in the treatment and prevention of a wide variety of central nervous system disorders, inflammatory disorders, cardiovascular disorders, ophthalmic disorders, etc.

IT **5392-11-0P**, 6-Methoxy-1-methyl-1H-quinolin-2-one
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; synthesis of benzoamide piperidine contg. compds. as substance P antagonists)

RN 5392-11-0 CAPLUS
CN 2(1H)-Quinolinone, 6-methoxy-1-methyl- (9CI) (CA INDEX NAME)

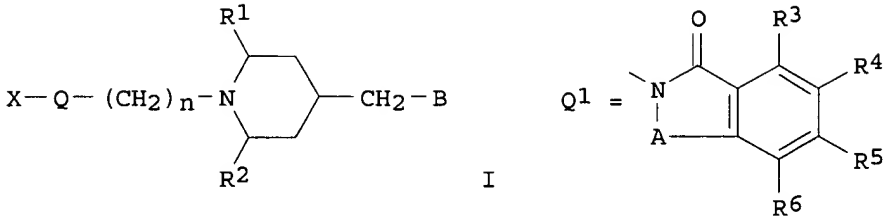


L5 ANSWER 2 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:661416 CAPLUS
DOCUMENT NUMBER: 135:226879
TITLE: Preparation of cyclic amide derivatives as sigma receptor ligands
INVENTOR(S): Yamabe, Haruko; Okuyama, Masahiro; Nakao, Akira; Ooizumi, Mitsuru; Saito, Ken-ichi
PATENT ASSIGNEE(S): Mitsubishi-Tokyo Pharmaceuticals, Inc., Japan
SOURCE: PCT Int. Appl., 259 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001064670	A1	20010907	WO 2001-JP1413	20010226

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: JP 2000-54674 A 20000229
OTHER SOURCE(S): MARPAT 135:226879
GI



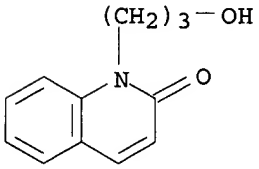
I

AB The title compds. I [X is alkyl, aryl, a heterocyclic group, etc.; Q is CH2, CO, O, etc.; n is an integer of 0 to 5; R1 and R2 are each hydrogen, alkyl, etc.; and B is Q1, etc.; A = (CH2)m; R3, R4, R5 and R6 are each hydrogen, halogeno, alkoxy, etc.; m is 1 or 2] are prepd. In an in vitro test for inhibition of sigma-2 receptor binding, 4-bromo-2-[[1-[2-(4-fluorophenyl)-2-oxoethyl]piperidin-4-yl]methyl]isoindolin-1-one hydrochloride showed the Ki value of 2.8 nM. Formulations are given.

IT **359629-69-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of cyclic amide derivs. as sigma receptor ligands)

RN 359629-69-9 CAPLUS

CN 2(1H)-Quinolinone, 1-(3-hydroxypropyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:581872 CAPLUS
DOCUMENT NUMBER: 135:147430
TITLE: 2-[1H]-quinolone and 2-[1H]-quinoxalone inhibitors of factor Xa, pharmaceutical compositions, and therapeutic use
INVENTOR(S): Zhu, Bing-Yan; Scarborough, Robert
PATENT ASSIGNEE(S): Cor Therapeutics, Inc., USA
SOURCE: PCT Int. Appl., 66 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001057021	A2	20010809	WO 2001-US3176	20010201
WO 2001057021	A3	20020214		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

S.1.E.

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-179389P P 20000201
US 2000-191722P P 20000324

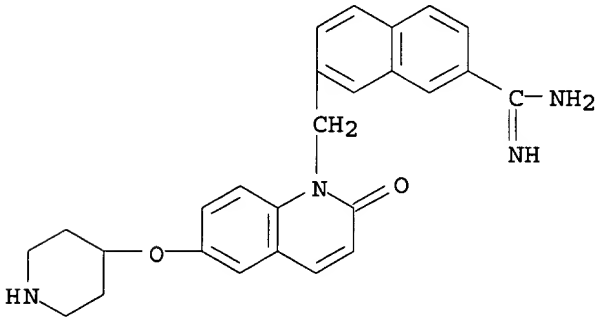
OTHER SOURCE(S): MARPAT 135:147430

AB The title compds. (Markush included), including their pharmaceutically acceptable isomers, salts, hydrates, solvates, and prodrug derivs., having activity against mammalian factor Xa, are described. Compns. contg. such compds. are also described. The compds. and compns. are useful in vitro or in vivo for preventing or treating conditions in mammals characterized by undesired **thrombosis**.

IT **353237-84-0**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(quinolone andquinoxalone inhibitors of factor Xa, pharmaceutical compns., and therapeutic use)

RN 353237-84-0 CAPLUS

CN 2-Naphthalenecarboximidamide, 7-[[2-oxo-6-(4-piperidinyloxy)-1(2H)-quinolinyl]methyl]- (9CI) (CA INDEX NAME)



L5 ANSWER 4 OF 61 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:537497 CAPLUS

DOCUMENT NUMBER: 135:122412

TITLE: Benzopyranone, dibenzopyranone, and quinolinone derivatives and analogs, useful as phospholamban inhibitors, and a method for increasing coronary flow

INVENTOR(S): Pystynen, Jarmo; Haikala, Heimo; Kaheinen, Petri; Kaivola, Juha; Pollesello, Piero; Ulmanen, Ismo; Tenhunen, Jukka; Tilgmann, Carola; Tiainen, Eija; Lonnberg, Kari; Nore, Pentti; Parhi, Seppo; Karjalainen, Arto; Levijoki, Jouko

PATENT ASSIGNEE(S): Orion Corporation, Finland

SOURCE: U.S., 35 pp., Cont.-in-part of U.S. Ser. No. 159,776, abandoned.
CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

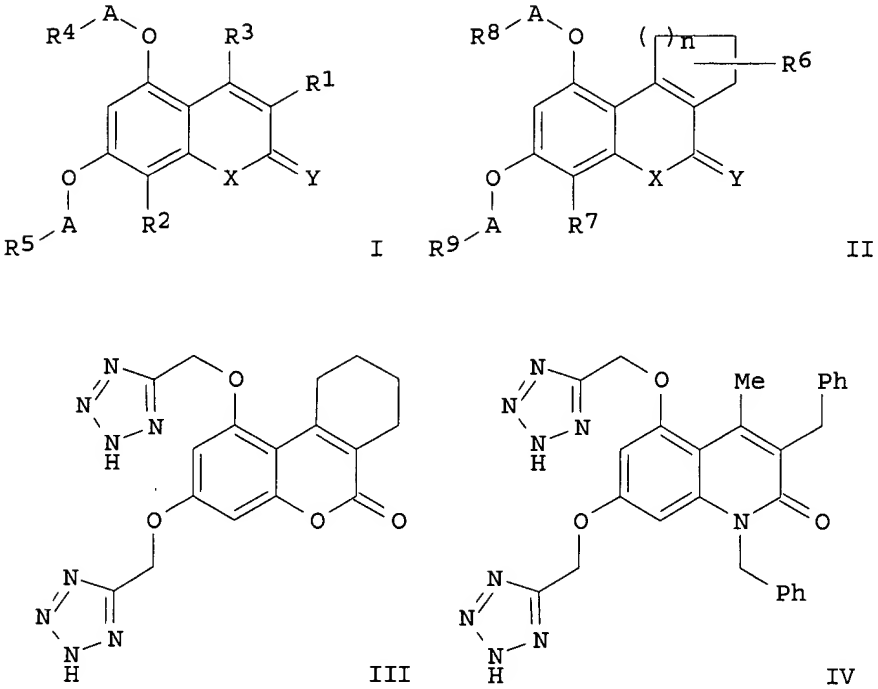
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6265421	B1	20010724	US 1999-252062	19990218
ZA 9805512	A	19990120	ZA 1998-5512	19980624
ZA 9808745	A	19990326	ZA 1998-8745	19980923

PRIORITY APPLN. INFO.: US 1997-882262 B2 19970625

US 1997-937118 B2 19970924
US 1997-937119 B2 19970924
US 1997-990150 B2 19971212
US 1998-104114 B2 19980625
US 1998-159776 B2 19980924

OTHER SOURCE(S): MARPAT 135:122412

GI



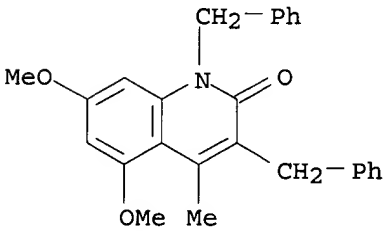
I II III IV

AB Three methods utilizing administration of a therapeutically effective amt. of a phospholamban inhibitor are claimed: (a) obtaining direct dilatation of the coronary arteries; (b) treatment of coronary heart disease; and (c) treatment of hemodynamic crisis, in which low aortic blood pressure decreases coronary perfusion pressure. Compds. which are effective in relieving the inhibitory effects of phospholamban on **cardiac** sarcoplasmic reticulum Ca2+-ATPase are also described. In particular, compds. I and II and their pharmaceutically acceptable salts and esters are claimed [wherein: R1 = H, alkyl, alkenyl, aryl, arylalkyl, hydroxyalkyl, haloalkyl, alkoxy, COR10, CONR10R11, OR10, S(O)mR10, NR10COR11, or NR10R11; R10 = H, alkyl, alkenyl, aryl, arylalkyl, hydroxyalkyl, haloalkyl, alkoxy or OH; R11 = H, alkyl, aryl, arylalkyl, alkoxy, aryloxy, OH, or acyl, or when X = NR11, R1 also = carboxyalkyl; R6 = H, alkyl, alkenyl, aryl, or arylalkyl; R2, R7 = H, alkyl, aryl, arylalkyl, alkenyl, COR10, CONR10R11, halo, CF3, nitro, or cyano; R3 = H, alkyl, aryl, or arylalkyl; A = alkyl or substituted alkyl; m = 0-2; n = 1-3; Y = O, NR11, or S; X = O, NR11, or S; R4, R5, R8, R9 = tetrazol-5-yl, 2-methyltetrazol-5-yl, 6(1H)-oxopyridazin-3-yl, oxooxadiazolyl (3 isomers), or 5-oxo-1,2,4-thiadiazol-3-yl; or where X = NR11 then R4, R5, R8 and R9 also = HOOC, R12OOC, H2NCO, or HOHNCO; R12 = alkyl, arylalkyl, or aryl; any aryl may be substituted]. Prepns. of 24 inhibitors are given, along with results of 7 biol. expts. For instance, acid-catalyzed cyclocondensation of phloroglucinol with Et 2-oxocyclohexanecarboxylate in 75% H2SO4 gave a tetrahydrodihydroxydibenzopyranone deriv., which was dietherified with 2 equiv chloroacetonitrile and further treated with NaN3

and NH4Cl to give title compd. III. In isolated guinea pig hearts, selected compds. I and II increased coronary blood flow with EC50 values of 0.9 to >10 .mu.M and max. effects of +38% to +174%, e.g., +100% for the quinolinone IV.

IT **219552-06-4P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; prepn. of benzopyranones and quinolinones as phospholamban inhibitors for increasing coronary blood flow)

RN 219552-06-4 CAPLUS
CN 2(1H)-Quinolinone, 5,7-dimethoxy-4-methyl-1,3-bis(phenylmethyl)- (9CI) (CA INDEX NAME)



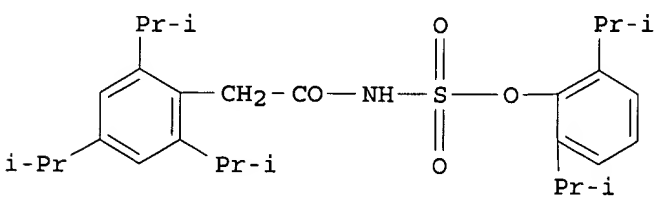
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 5 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:359777 CAPLUS
DOCUMENT NUMBER: 134:371771
TITLE: Prevention of plaque rupture by ACAT inhibitors
INVENTOR(S): Bocan, Thomas Michael Andrew
PATENT ASSIGNEE(S): Warner-Lambert Company, USA
SOURCE: PCT Int. Appl., 108 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001034127	A1	20010517	WO 2000-US28705	20001017

W: AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, MZ, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-163814P P 19991105
OTHER SOURCE(S): MARPAT 134:371771
GI



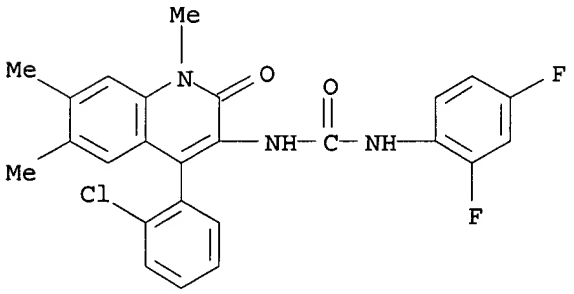
I

AB This invention is the administration of an ACAT inhibitor to prevent monocyte-macrophage accumulation and MMP expression in atherosclerotic lesions. Further, this invention relates to methods of inhibiting destabilization and/or rupture of atherosclerotic plaques and treatment of unstable **angina**. Tablets were prepd. contg. a ACAT inhibitor such as I.

IT **136280-68-7**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prevention of plaque rupture by ACAT inhibitors)

RN 136280-68-7 CAPLUS

CN Urea, N-[4-(2-chlorophenyl)-1,2-dihydro-1,6,7-trimethyl-2-oxo-3-quinolinyl]-N'-(2,4-difluorophenyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 6 OF 61 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:268246 CAPLUS

DOCUMENT NUMBER: 135:86881

TITLE: Antiplatelet and antithrombotic activity of SL65.0472, a mixed 5-HT1B/5-HT2A receptor antagonist

AUTHOR(S): Berry, Christopher N.; Lorrain, Janine; Lochot, Sylvette; Delahaye, Monique; Lale, Alain; Savi, Pierre; Lechaire, Irene; Ferrari, Patrice; Bernat, Andre; Schaeffer, Paul; Janiak, Philippe; Duval, Nicole; Grosset, Alain; Herbert, Jean-Marc; O'Connor, Stephen E.

CORPORATE SOURCE: Cardiovascular/Thrombosis Department, Sanofi.apprx.Synthelabo, Chilly Mazarin, 91385, Fr.

SOURCE: Thrombosis and Haemostasis (2001), 85(3), 521-528
CODEN: THHADQ; ISSN: 0340-6245

PUBLISHER: F. K. Schattauer Verlagsgesellschaft mbH

DOCUMENT TYPE: Journal

LANGUAGE: English

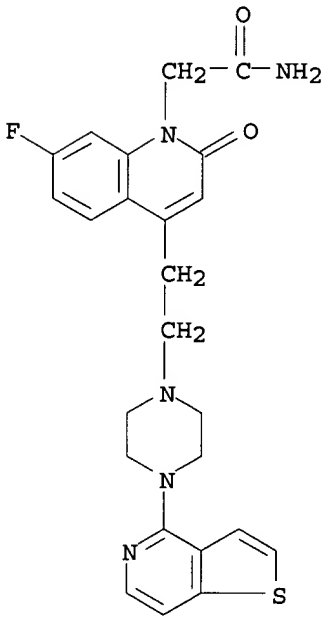
AB The antiplatelet and antithrombotic activity of SL65.0472 (7-fluoro-2-oxo-4-[2-[4-(thieno[3,2-c]pyrin-4-yl)piperazin-1-yl]ethyl]-1,2-dihydroquinoline-acetamide), a mixed 5-HT1B/5-HT2A receptor antagonist was investigated on 5HT-induced human platelet activation in vitro, and in rat, rabbit and canine platelet dependent **thrombosis** models. SL65.0472 inhibited 5-HT-induced platelet shape change in the presence of EDTA (IC50 values = 35, 69 and 225 nM in rabbit, rat and human platelet rich plasma (PRP)), and also inhibited aggregation induced in human PRP by 3-5 .mu.M 5-HT + threshold concns. of ADP (0.5-1 .mu.M) or collagen (0.3 .mu.g/mL) with mean IC50 values of 49.+-.13 and 48.+-.6 nM resp. SL65.0472 inhibited **thrombus** formation when given both i.v. 5 min and orally 2 h prior to assembly of an arterio-venous (A-V) shunt in rats as from 0.1 and 0.3 mg/kg resp. It was active in a rabbit A-V shunt model with significant decreases in **thrombus** wt. as from 0.1

mg/kg i. v. and at 10 mg/kg p. o. The delay to occlusion in an elec. current-induced rabbit femoral artery **thrombosis** model was increased by 251% (p <0.05) after 20 mg/kg p. o: SL65.0472 (30 .mu.g/kg i. v.) virtually abolished coronary cyclic flow variations (7.2.+-.1.0/h to 0.6.+-.0.6/h, p <0.05) and increased min. coronary blood flow (1.2.+-.0.8 mL/min to 31.8.+-.8.4 mL/min, p <0.05) in a coronary artery **thrombosis** model in the anesthetized dog. Finally, SL65.0472 significantly increased the amt. of blood lost after rat tail transection at 3 mg/kg p. o. Thus the anti-5-HT2A component of SL65.0472 is reflected by its ability to inhibit 5-HT-induced platelet activation, and platelet-rich **thrombus** formation.

IT **189003-92-7**, SL650472
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiplatelet and antithrombotic activity of SL65.0472, a mixed 5-HT1B/5-HT2A receptor antagonist)

RN 189003-92-7 CAPLUS

CN 1(2H)-Quinolineacetamide, 7-fluoro-2-oxo-4-[2-(4-thieno[3,2-c]pyridin-4-yl-1-piperazinyl)ethyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

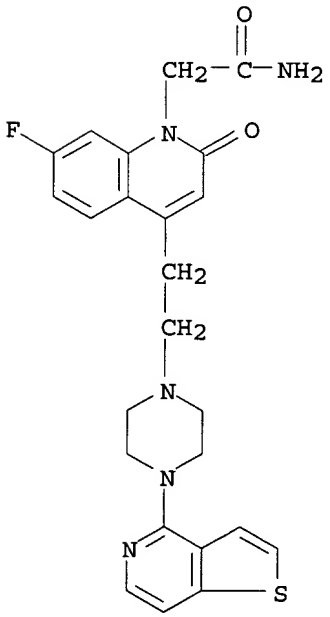
L5 ANSWER 7 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:164201 CAPLUS
DOCUMENT NUMBER: 135:40706
TITLE: Cardiovascular effects of SL65.0472, a 5-HT receptor antagonist
AUTHOR(S): O'Connor, S. E.; Grosset, A.; Drieu La Rochelle, C.; Gautier, E.; Bidouard, J.-P.; Robineau, P.; Caille, D.; Janiak, P.
CORPORATE SOURCE: Cardiovascular/Thrombosis Research Department, Sanofi-Synthelabo, Chilly-Mazarin, 91385, Fr.
SOURCE: European Journal of Pharmacology (2001), 414(2/3), 259-269
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal
LANGUAGE: English

AB In this study, we describe the cardiovascular effects of SL65.0472 (7-fluoro-2-oxo-4-[2-[4-(thieno[3,2-c]pyridin-4-yl)piperazin-1-yl] ethyl]-1,2-dihydroquinoline-1-acetamide), a novel 5-hydroxytryptamine (5-HT) receptor antagonist developed for the treatment of cardiovascular disease, in several in vivo models. The hemodynamic profile of SL65.0472 was evaluated in anesthetized dogs. Following i.v. bolus doses of 0.03 mg/kg i.v. and 0.3 mg/kg, no significant changes in **cardiac** output, contractility or rate, systemic and pulmonary pressures, regional blood flows and vascular resistances or ECG were noted. After 1 mg/kg i.v. SL65.0472 significantly reduced arterial blood pressure. In conscious spontaneously hypertensive rats administration of SL65.0472 0.5 mg/kg p.o. had no effect on mean arterial blood pressure or heart rate. Vasoconstriction produced by 5-HT results primarily from the stimulation of two receptor subtypes, 5-HT1B and 5-HT2A receptors. In anesthetized dogs SL65.0472 antagonized sumatriptan-induced decreases in saphenous vein diam. (5-HT1B-receptor mediated) with an ID50 of 10.1 .mu.g/kg i.v. (95% c.l. 8.3-12.4). In anesthetized pithed rats SL65.0472 inhibited 5-HT pressor responses (5HT2A-receptor mediated) with ID50 values of 1.38 .mu.g/kg i.v. (95% c.l. 1.15-1.64) and 31.1 .mu.g/kg p.o. (95% c.l. 22.6-42.6). The duration of the 5-HT2A-receptor antagonist effect of SL65.0472 following oral administration was evaluated in conscious rats. SL65.0472 (0.1 mg/kg p.o.) markedly inhibited 5-HT pressor responses 1 and 6 h after administration. Therefore, in vivo, SL65.0472 potently antagonizes vasoconstriction mediated by 5-HT1B and 5-HT2A receptors but has minimal direct hemodynamic effects.

IT **189003-92-7**, SL 650472
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cardiovascular effects of SL65.0472, a 5-HT receptor antagonist)

RN 189003-92-7 CAPLUS
CN 1(2H)-Quinolineacetamide, 7-fluoro-2-oxo-4-[2-(4-thieno[3,2-c]pyridin-4-yl-1-piperazinyl)ethyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 8 OF 61 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:404487 CAPLUS

DOCUMENT NUMBER: 133:12686

TITLE: Linomide in relapsing and secondary progressive MS. Part I: trial design and clinical results

AUTHOR(S): Noseworthy, J. H.; Wolinsky, J. S.; Lublin, F. D.; Whitaker, J. N.; Linde, A.; Gjorstrup, P.; Sullivan, H. C.; Whitaker, John; Mitchell, Galen; LaGanke, Chris; Layton, Beverly; Sibley, William A.; Sherman, Scott; Geisser, Barbara; Kunkel-Thomas, Jean; Mar, Janet; McGregor, Todd; Jeffrey, Douglas R.; Troost, B. Todd; Leftkowitz, D.; McKinney, William; Harris, Lorraine; Jacobs, Lawrence; Pordell, Reza; Munschauer, Frederick E.; Doherty, Elizabeth; Greenberg, Steven J.; Krantz, Susan; Agius, Mark A.; Richman, David; Vijayan, N.; Kyu, Lee Eun; Adams, Janelle; Myers, Lawrence; Girard, Joanna; Baumhefner, Robert; Rosner, Louis; Craig, Sharon; Reder, Anthony; Noronha, Avertano; Arnason, Barry; Jacobs, Gwen; Richert, John; Tornatore, Carlo; Kres-Reahl, Kiren; Kattah, Jorge; Pachner, Andrew; Gustafson, Tarah; Rice, George; Ebers, George; Koopman, Wilma; Vandervoort, Margaret; Miller, Aaron; Keilson, Marshall; Bruining, Kersti; Drexler, Ellen; Sciarra, Linda; Apatoff, Brian; Singer, Barry; Wheatley, Justine; Periconi, Priscilla; Bever, Christopher, Jr.; Johnson, Kenneth P.; Khan, Omar; Panitch, Hillel; Jalbut, Suhayl; Katz, Eleanor; Conway, Cathy; Noseworthy, John H.; Lucchinetti, Claudia; Weinshenker, Brian; Rodriguez, Moses; Adams, Andrea; Arneson, Melinda; Carter, Jonathan L.; Caselli, Richard; Hirschorn, Kathryn J.; Ingall, Timothy J.; Metcalf, Alycia; Meshulam, Carrie; Cohen, Jeffrey; Masaryk, Thomas; Guttmann, Bianca; Kinkel, Revere P.; Rudick, Richard; Adler, Patricia; Birnbaum, Gary; Shapiro, Randall; Knopman, David; See, Crispin; Nelson, Rosemary; Lublin, Fred D.; Trantas, Flo; Kelly, Leith; Francis, Gordon; Barkas, William; Lapierre, Yves; Arnaoutelis, Rozie; Cook, Stuart; Bansil, Shalini; Picone, Mary Ann; Jotkowitz, Annette; Quinless, James; Metz, Luanne; Patry, David; Bell, Robert; Murphy, W. F.; Pitts, Amanda; McGuinness, Sandra; Goodman, Andrew; Mattson, David H.; Schwid, Steven R.; Scheid, Eileen; Stefoski, Dusan; Davis, Floyd A.; Karlin, Karyn; Rush, Jean; Podraza, Greg; O'Connor, Paul W.; Gray, Trevor; Marchetti, Paul; Hall, Julie; Coyle, Patricia K.; Krupp, Lauren; Gerber, O.; Doscher, Carol; Wolinsky, Jerry S.; Lindsey, William; Brod, Staley; Dimachkie, Mazen; Cerreta, Emily; Howard, Jane E.; Sriram, Subramanian; Kirshner, Howard; Browning, Renee; Lisak, Robert P.; Tselis, Alex C.; Kamholtz, John; Garbern, James; Lewis, Richard; Tvardek, Linda; Linde, Anders; Gjorstrup, Per; Sullivan, Herman; McFarland, Henry F.; Flexnor, Charles; Hauser, Stephen L.; Carter, Walter H., Jr.; Petkau, John; Reingold, Stephen

CORPORATE SOURCE: Department of Neurology, Mayo Clinic/Mayo Foundation, Rochester, MN, 55905, USA

SOURCE: Neurology (2000), 54(9), 1726-1733
CODEN: NEURAI; ISSN: 0028-3878

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

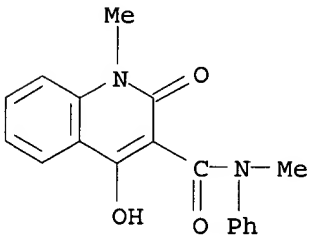
LANGUAGE: English

AB Objective: To det. whether linomide (roquinimex) is better than placebo in slowing the time to confirmed clin. worsening in patients with relapsing-remitting (RR) and secondary progressive (SP) MS. Methods: In this 27-center, randomized, double-blind, placebo-controlled, multiple-dose, phase III trial, 715 patients with active RRMS (n = 90) or SPMS (n = 625) were randomized to receive either linomide (1.0, 2.5, or 7.5 mg orally daily) or placebo. Patients were evaluated at 3-mo intervals clin. and with MRI. The planned primary outcome was the time to the development of "confirmed" clin. worsening (increase of .gtoreq. 1.0 Expanded Disability Status Scale [EDSS] score for an enrollment EDSS score .ltoreq. 5.0, or .gtoreq. 0.5 point for an enrollment EDSS score of .gtoreq. 5.5) not assocd. with an acute relapse. Results: The trial was terminated 1 mo after it became fully enrolled due to unanticipated serious cardiopulmonary toxicities (pericarditis, pleural effusion, myocardial **infarction**, and possible pulmonary embolism), pancreatitis, and death. Notable arthralgia, myalgia, bursitis, and facial and peripheral edema were common adverse events. The high dose of linomide (7.5 mg) was not well tolerated. The trial was too brief to det. unequivocal clin. benefits. Trends suggested an unconfirmed early effect on change in EDSS score at 6 mo for the medium dose (2.5 mg daily). Conclusion: MS patients may be more prone to develop important linomide treatment-related adverse events than other previously studied patients. However, linomide may be a potentially more toxic drug than was suspected from observations made in smaller studies for other indications. Phase III trials may identify infrequent and important toxicities that may not be anticipated by phase I and II trials.

IT **84088-42-6**, Linomide
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(linomide in relapsing and secondary progressive multiple sclerosis in humans, Part I: trial design and clin. results)

RN 84088-42-6 CAPLUS

CN 3-Quinolinecarboxamide, 1,2-dihydro-4-hydroxy-N,1-dimethyl-2-oxo-N-phenyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 9 OF 61 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:384173 CAPLUS

DOCUMENT NUMBER: 133:3766

TITLE: Isolation of SF2809-I, II, III, IV, V and VI substances exhibiting chymase-inhibiting activities from Dactylosporangium

INVENTOR(S): Tani, Masato; Gyobu, Yasuhiro; Moriyama, Chieko; Sasaki, Toru; Takenouchi, Osami; Kawamura, Takashi; Kamimura, Takashi; Harada, Toshiaki

PATENT ASSIGNEE(S): Meiji Seika Kaisha, Ltd., Japan; Teijin Ltd.

SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2

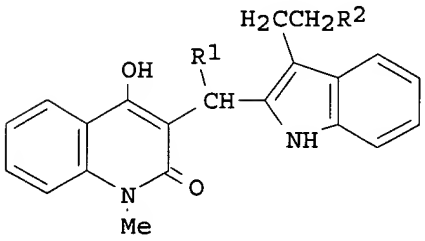
09/ 773,374

DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000032587	A1	20000608	WO 1999-JP6738	19991201
W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1136488	A1	20010926	EP 1999-973023	19991201
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: JP 1998-341523 A 19981201
WO 1999-JP6738 W 19991201

GI



I

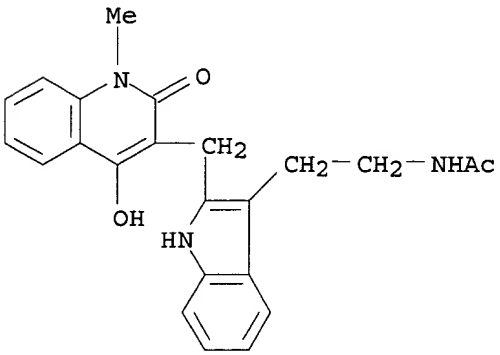
AB Novel compds. exhibiting chymase-inhibiting activities and being useful as various drugs, i.e., SF2809-I, SF2809-II, SF2809-III, SF2809-IV, SF2809-V and SF2809-VI substances represented by general formula [I; wherein R1 is hydrogen, Ph or p-hydroxyphenyl; and R2 is acetylamino (NHCOCH3) or hydroxyl] or pharmaceutically acceptable salts thereof are isolated from fermn. broth of Dactylosporangium. They are useful for the treatment or prevention of myocardial **infarction**, **cardiac** hypertrophy, cardiomyopathy, arteriosclerosis, hypertension, endovascular thickening, peripheral circulation disorders, kidney failure, inflammation, allergies, atopic dermatitis, rheumatism, asthma, and bronchitis. Thus, Dactylosporangium was aerobically cultured in a medium contg. glucose 2.0, sol. starch 1.0, soybean meal 1.5, polypeptone 0.1, wheat germ 0.8, staminol 0.1, NaCl 0.1, and CaCO3 0.2 (adjusted to pH 8.0 with 6 N NaOH) with stirring at 28.degree. for 5 days. The fermn. liq. (120 L) was centrifuged to sep. the microorganism. The supernatant liq. was extd. with EtOAc. The microorganism was extd. with 50% acetone and the acetone was distd. out from the filtrate under reduced pressure, followed by extn. with EtOAc. The combined EtOAc ext. was concd. in vacuo to give 56 g ext. which was washed with hexane, dissolved in MeOH, and purified by chromatog. using Sephadex LH-20 and Cosmosil column and HPLC to give SF2809-I 2.3, SF2809-II 1.3, SF2809-III 2.3, SF2809-IV 2.7, SF2809-V 1.1 and SF2809-VI 1.0 mg. The combined ext. was. SF2809-I, II, III, IV, V and VI showed IC50 of 7.3.times.10-6, 4.1.times.10-8, 2.1.times.10-6, 8.1.times.10-8, 4.3.times.10-8, 4.3.times.10-8, and 1.4.times.10-8 M against human chymase.

IT **271580-72-4P**
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BPN (Biosynthetic preparation); BSU (Biological study,

unclassified); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); USES (Uses)
(isolation of SF2809-I, II, III, IV, V and VI substances exhibiting chymase-inhibiting activities from Dactylosporangium as drugs)

RN 271580-72-4 CAPLUS

CN Acetamide, N-[2-[2-[(1,2-dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolinyl)methyl]-1H-indol-3-yl]ethyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 10 OF 61 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:161119 CAPLUS

DOCUMENT NUMBER: 132:203174

TITLE: Inhibitors of p38-.alpha. kinase, preparation thereof, and therapeutic use

INVENTOR(S): Goehring, R. Richard; Luedtke, Gregory R.; Mavunkel, Babu J.; Chakravarty, Sarvajit; Dugar, Sundeep; Schreiner, George F.; Liu, David Y.; Lewicki, John A.

PATENT ASSIGNEE(S): Scios Inc., USA

SOURCE: PCT Int. Appl., 75 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

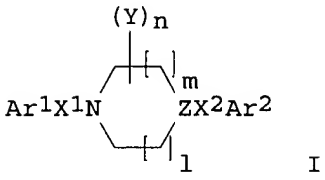
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000012074	A2	20000309	WO 1999-US19845	19990827
WO 2000012074	A3	20000831		
W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, EE, GE, HU, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9957936	A1	20000321	AU 1999-57936	19990827
EP 1107758	A2	20010620	EP 1999-945316	19990827
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 9913654	A	20011127	BR 1999-13654	19990827

PRIORITY APPLN. INFO.:

US 1998-98219P	P	19980828
US 1999-125343P	P	19990319
US 1998-125343P	P	19990319
WO 1999-US19845	W	19990827

09/ 773,374

OTHER SOURCE(S): MARPAT 132:203174
GI



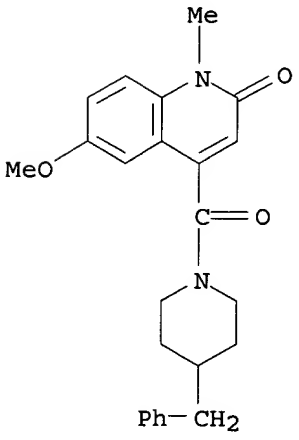
I

AB Methods are provided for treating conditions mediated by p38-.alpha. kinase using compds. I (Z = N, CR1; R1 = noninterfering substituent; X1, X2 = linker; Ar1, Ar2 = (un)substituted C1-20 hydrocarbyl (at least one of Ar1 and Ar2 = (un)substituted aryl), with proviso that when X2 = CH2 or an isostere thereof, X1 = CO or an isostere thereof, and Ar2 = (un)substituted Ph, Ar1 is other than (un)substituted indolyl, benzimidazolyl or benzotriazolyl, and wherein (un)substituted Ph is not (un)substituted indolyl, benzimidazolyl, or benzotriazolyl; Y = noninterfering substituent; n, m = 0-4; l = 0-3) or a pharmaceutically acceptable salt or pharmaceutical compn. thereof. Prepn. of compds. is described. Compds. of the invention may be used to treat p38-.alpha. kinase-mediated conditions.

IT **260427-90-5**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(p38-.alpha. kinase inhibitors, prepn., and therapeutic use)

RN 260427-90-5 CAPLUS

CN Piperidine, 1-[(1,2-dihydro-6-methoxy-1-methyl-2-oxo-4-quinolinyl)carbonyl]-4-(phenylmethyl)- (9CI) (CA INDEX NAME)



L5 ANSWER 11 OF 61 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:144089 CAPLUS

DOCUMENT NUMBER: 132:180491

TITLE: Preparation of 2-oxo-2H-quinolines as Factor Xa inhibitors.

INVENTOR(S): Mederski, Werner; Juraszyk, Horst; Wurziger, Hanns; Dorsch, Dieter; Gante, Joachim; Buchstaller, Hans-Peter; Bernotat-Danielowski, Sabine; Melzer,

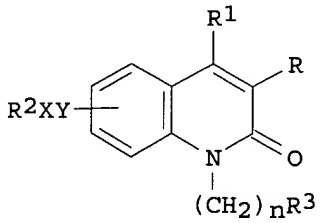
09/ 773,374

	Guido; Anzali, Soheila
PATENT ASSIGNEE(S):	Merck Patent G.m.b.H., Germany
SOURCE:	Ger. Offen., 16 pp.
	CODEN: GWXXBX
DOCUMENT TYPE:	Patent
LANGUAGE:	German
FAMILY ACC. NUM. COUNT:	1
PATENT INFORMATION:	

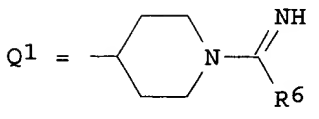
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19839499	A1	20000302	DE 1998-19839499	19980829
WO 2000012479	A1	20000309	WO 1999-EP5315	19990726
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9951641	A1	20000321	AU 1999-51641	19990726
BR 9913140	A	20010508	BR 1999-13140	19990726
EP 1107954	A1	20010620	EP 1999-936606	19990726
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
NO 2001000996	A	20010227	NO 2001-996	20010227

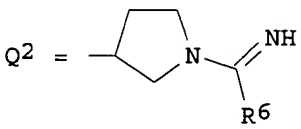
PRIORITY APPLN. INFO.:		DE 1998-19839499 A	19980829
		WO 1999-EP5315 W	19990726
OTHER SOURCE(S):	MARPAT 132:180491		

GI



I





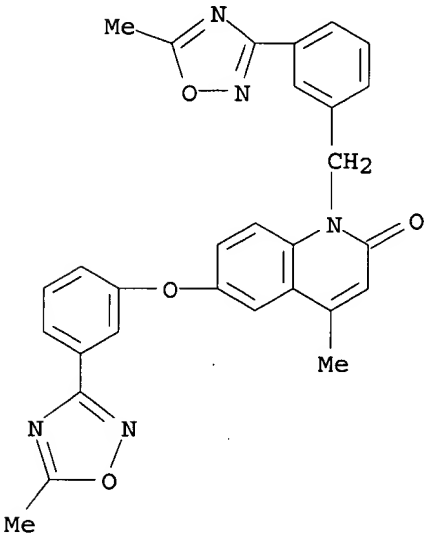
AB Title compds. [I; R, R1 = H, A, (CH2)mR4, (CH2)mOA, (CH2)mAr; R2 = Ar, Q1, Q2; R3 = Ar; R4 = cyano, CO2H, CO2A, CONH2, CONHA, CCONA2, C(:NH)NH2; R6 = H, A, NH2; Ar = (substituted) Ph, naphthyl, biphenyl; A = alkyl; X = null, alkylene, CO; Y = null, NH, O, S; m = 0-2; n = 0-3], were prepd. as cardiovascular agents (no data). Thus, N-[4-[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenoxy]phenyl]-3-oxobutyramide (prepn. given) was heated in H2SO4 at 80.degree. to give 6-[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenoxy]-4-methyl-2-oxo-2H-quinoline. This was stirred with NaOCMe3 in DMF followed by addn. of 3-(3-bromomethylphenyl)-5-methyl-1,2,4-oxadiazole to give 1-[3-(5-methyl-1,2,4-oxadiazol-3-yl)benzyl]-6-[3-(5-methyl-1,2,4-oxadiazol-

3-yl)phenoxy]-4-methyl-2-oxo-2H-quinoline. The latter was hydrogenated in MeOH contg. HOAc over Raney Ni to give 1-(3-amidinobenzyl)-6-(3-amidinophenoxy)-4-methyl-2-oxo-2H-quinoline.

IT **259184-25-3P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 2-oxo-2H-quinolines as Factor Xa inhibitors)

RN 259184-25-3 CAPLUS

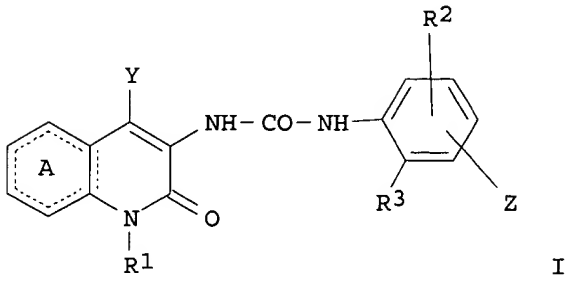
CN 2(1H)-Quinolinone, 4-methyl-6-[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenoxy]-1-[[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]methyl]- (9CI) (CA INDEX NAME)



L5 ANSWER 12 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:133678 CAPLUS
DOCUMENT NUMBER: 132:180562
TITLE: Preparation of naphthyridine derivatives as acyl-CoA:cholesterol acyltransferase (ACAT) inhibitors
INVENTOR(S): Muraoka, Masami; Ban, Hitoshi; Ohashi, Naohito
PATENT ASSIGNEE(S): Sumitomo Pharmaceuticals Co., Ltd., Japan
SOURCE: PCT Int. Appl., 95 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000009505	A1	20000224	WO 1999-JP4257	19990805
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9950659	A1	20000306	AU 1999-50659	19990805
EP 1104763	A1	20010606	EP 1999-935084	19990805

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO
PRIORITY APPLN. INFO.: JP 1998-226685 A 19980811
WO 1999-JP4257 W 19990805
OTHER SOURCE(S): MARPAT 132:180562
GI



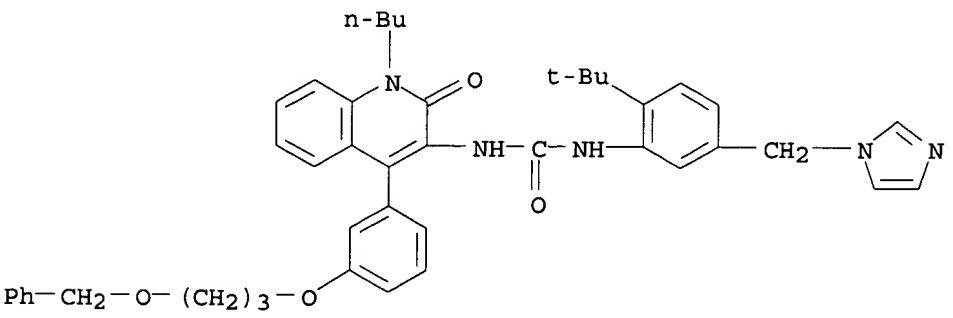
I

AB Title compds. I [ring A represents an optionally substituted pyridine ring; Y represents optionally substituted alkyl, etc.; R1 represents hydrogen, optionally substituted alkyl, etc.; R2 represents hydrogen or lower alkyl; R3 represents lower alkyl; and Z represents: (1) D1Q (wherein D1 represents a bond, divalent C1-8 hydrocarbyl, etc.; and Q represents hydroxy, carboxy, etc.); or (2) D2MEW (wherein D2 represents a bond, a divalent C1-8 hydrocarbyl, etc.; M represents oxygen, sulfur, etc.; E represents a bond, divalent C1-8 hydrocarbyl, etc.; and W represents hydroxy, carboxy, etc.)] are prepd. and as remedies for hyperlipemia and arteriosclerosis. The title compd. N-[1-butyl-4-(3-methoxyphenyl)-1,2-dihydro-2-oxo-1,8-naphthyridin-3-yl]-N'-[2-tert-butyl-5-(morpholinomethyl)phenyl]urea hydrochloride in vitro at 10-6 M gave 98% inhibition of ACAT.

IT **259224-86-7P**
RL: BAC (Biological activity or effector, except adverse); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of naphthyridine derivs. as ACAT inhibitors)

RN 259224-86-7 CAPLUS

CN Urea, N-[1-butyl-1,2-dihydro-2-oxo-4-[3-[3-(phenylmethoxy)propoxy]phenyl]-3-quinolinyl]-N'-[2-(1,1-dimethylethyl)-5-(1H-imidazol-1-ylmethyl)phenyl]-(9CI) (CA INDEX NAME)

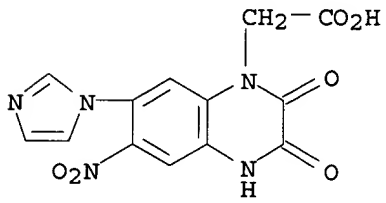


REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 13 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:54684 CAPLUS
DOCUMENT NUMBER: 132:329238
TITLE: YM-872, Yamanouchi
AUTHOR(S): Danysz, Wojciech
CORPORATE SOURCE: Department of Pharmacological Research, Merz and Co., Frankfurt/Main, 60318, Germany
SOURCE: IDrugs (2000), 3(1), 84-89
CODEN: IDRUFN; ISSN: 1369-7056
PUBLISHER: Current Drugs Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 44 refs. Yamanouchi is developing YM-872, an AMPA receptor antagonist, as a potential treatment for cerebrovascular ischemia. It entered phase II trials in Europe in August 1998. It is undergoing phase I trials in Japan and was in phase II trials in the US as of August 1998. Yamanouchi hopes that YM-872 will be eligible for priority review and approval because of its new mechanism of action and the great medical need for such a drug. YM-872, an N-carboxymethyl deriv., displayed potent AMPA receptor affinity (Ki = 95 nM) and antikainate effect (IC50 = 0.8 .mu.M) and was >500-fold more sol. than its parent compd. YM-90K, allowing i.v. administration in a lower vol. of infusion. Neuroprotective effects have been obsd. in a rat model of permanent focal ischemia. When given by infusion (20 mg/kg/h over 4 h), 1 h after exptl. ischemia, the drug was neuroprotective in the cortex (but not striatum) when measured 24 h after the ischemic insult. YM-872 has neuroprotective properties and ameliorates the deterioration of the hemodynamic penumbra by reducing the perfusion threshold for **infarction** after an episode of permanent focal ischemia. YM-872 reduced the atrophy of the substantia nigra in rats following middle cerebral artery occlusion. The therapeutic window of opportunity for YM-872 is 3 h in the above model.

IT **210245-80-0P**, YM 872
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(pharmacol. of YM-872)
RN 210245-80-0 CAPLUS
CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 14 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:39234 CAPLUS
DOCUMENT NUMBER: 132:87574
TITLE: YM-872 Yamanouchi
AUTHOR(S): Danysz, Wojciech
CORPORATE SOURCE: Department of Pharmacological Research, Merz and Co., Frankfurt/Main, Germany
SOURCE: Current Opinion in Cardiovascular, Pulmonary & Renal Investigational Drugs (1999), 1(5), 677-682

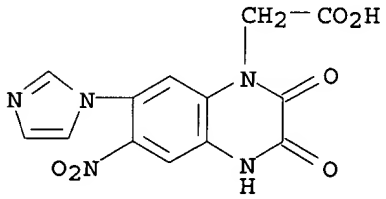
CODEN: CCPRFX; ISSN: 1464-8482
PUBLISHER: Current Drugs Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 44 refs. Yamanouchi is developing YM-872, an AMPA receptor antagonist, as a potential treatment for cerebrovascular ischemia. It entered phase II trials in Europe in August 1998 [295049]. It is undergoing phase I trials in Japan [270568] and was in phase II trials in the US as of August 1998 [295049]. Yamanouchi hopes that YM-872 will be eligible for priority review and approval because of its new mechanism of action and the great medical need for such a drug [343645]. YM-872, an N-carboxymethyl deriv., displayed potent AMPA affinity (Ki = 95 nM), anti-kainate effect (IC50 = 0.8 .mu.M) and was over 500-fold more sol. than its parent compd. YM-90K, allowing iv administration in a lower vol. of infusion [228599,294636]. Neuroprotective effects have been obsd. in a rat model of permanent focal ischemia. When given by infusion (20 mg/kg/h over 4 h), 1 h after exptl. ischemia, the drug was neuroprotective in the cortex (but not striatum) when measured 24 h after the ischemic insult. YM-872 has neuroprotective properties and ameliorates the deterioration of the hemodynamic penumbra by reducing the perfusion threshold for **infarction** after an episode of permanent focal ischemia [254092]. YM-872 significantly reduced the atrophy of the substantia nigra in rats following middle cerebral artery occlusion (MCAO) [307119]. The therapeutic window of opportunity for YM-872 is 3 h in the above model [324580]. In Feb. 1999, Lehman Brothers predicted the first major product launch to be in 2004, with sales peaking in 2012 [319225].

IT **210245-80-0**, YM 872
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(YM-872 cerebrovascular anti-ischemic profile of)

RN 210245-80-0 CAPLUS

CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 15 OF 61 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:7543 CAPLUS
DOCUMENT NUMBER: 132:202991

TITLE: Neuroprotective effects of an AMPA receptor antagonist YM872 in a rat transient middle cerebral artery occlusion model

AUTHOR(S): Kawasaki-Yatsugi, S.; Ichiki, C.; Yatsugi, S.-i.; Takahashi, M.; Shimizu-Sasamata, M.; Yamaguchi, T.; Minematsu, K.
CORPORATE SOURCE: Institute for Drug Discovery Research, Pharmacology Laboratories, Neuroscience Research, Yamanouchi Pharmaceutical Co., Ltd., Tsukuba, Ibaraki, Japan

SOURCE: Neuropharmacology (2000), 39(2), 211-217
CODEN: NEPHBW; ISSN: 0028-3908
PUBLISHER: Elsevier Science Ltd.

09/ 773,374

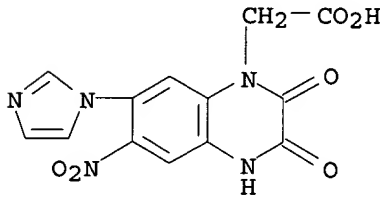
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The neuroprotective effects of YM872 ([2,3-dioxo-7-(1H-imidazol-1-yl)6-nitro-1,2,3,4-tetrahydro-1-quinoxalinyl]acetic acid monohydrate), a novel .alpha.-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) receptor antagonist with high water soly., were examd. in rats with transient middle cerebral artery (MCA) occlusion. The right MCA of male SD rats was occluded for 3 h using the intraluminal suture occlusion method. YM872 significantly reduced the **infarct** vol. 24 h after occlusion, at dosages of 20 and 40 mg/kg/h (iv infusion) when given for 4 h immediately after occlusion. Furthermore, delayed administration of YM872 (20 mg/kg/h iv infusion for 4 h, starting 2 or 3 h after the occlusion) also reduced the **infarct** vol. and the neurol. deficits measured at 24 h. Addnl., the therapeutic efficacy of YM872 persisted for at least seven days after MCA occlusion in animals treated with YM872 for 4 h starting 2 h after MCA occlusion. These data demonstrate that AMPA receptors contribute to the development of neuronal damage after reperfusion as well as during ischemia in the focal ischemia models and that the acute effect of the blockade of AMPA receptors persists over a long time period. YM872 shows promise as an effective treatment for patients suffering from acute stroke.

IT **210245-80-0**, YM872
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neuroprotective effects of an AMPA receptor antagonist YM872 in a rat transient middle cerebral artery occlusion model)

RN 210245-80-0 CAPLUS

CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)

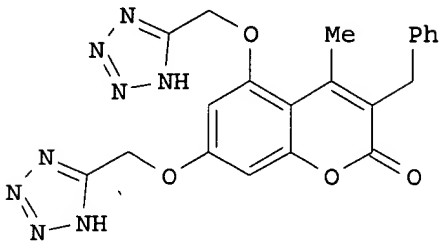


REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 16 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:670118 CAPLUS
DOCUMENT NUMBER: 131:286418
TITLE: A method for the prevention and treatment of stunned myocardium using benzopyranones, quinolinones, and other phospholamban inhibitors
INVENTOR(S): Haikala, Heimo; Kaheinen, Petri; Levijoki, Jouko; Kaivola, Juha; Ovaska, Martti; Pystynen, Jarmo
PATENT ASSIGNEE(S): Orion Corp., Finland
SOURCE: U.S., 29 pp., Cont.-in-part of U. S. Ser. 990,146, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5968959	A	19991019	US 1998-188707	19981110

ZA 9811180 A 19990609 ZA 1998-11180 19981207
PRIORITY APPLN. INFO.: US 1997-990146 B2 19971212
GI



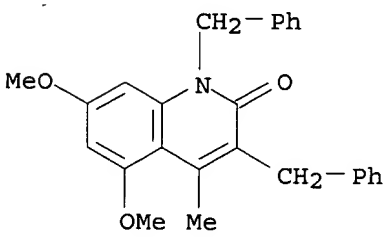
I

AB A method for the prevention and treatment of stunning of the heart subsequent to ischemia-reperfusion or resulting from unstable **angina** or valvular heart disease is described. The method comprises administering a therapeutically effective amt., preferably 0.5 to 50 mg per day, of a phospholamban inhibitor to a patient. Phospholamban inhibitors relieve the inhibitory effect of phospholamban on **cardiac** sarcoplasmic reticulum Ca2+-ATPase. Prepns. of 24 inhibitors are given, along with results of 3 biol. expts. For instance, acid-catalyzed cyclocondensation of phloroglucinol dihydrate with Et 2-benzylacetoacetate (96%), followed by bis-O-alkylation with ClCH2CN (88%), and cyclization of the nitriles with NaN3 in the presence of NH4Cl (81%), gave title compd. (I). This compd., at 100 .mu.M in vitro, gave a 42% stimulation of Ca2+ uptake into **cardiac** vesicles prepd. from guinea pig ventricular myocardium contg. phospholamban, but a 6% inhibition of Ca2+ uptake into fast skeletal muscle vesicles which do not contain it.

IT **219552-06-4P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation) (intermediate; prepn. of benzopyranones and quinolinones as phospholamban inhibitors for the prevention and treatment of stunned myocardium)

RN 219552-06-4 CAPLUS

CN 2(1H)-Quinolinone, 5,7-dimethoxy-4-methyl-1,3-bis(phenylmethyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 17 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:640853 CAPLUS
DOCUMENT NUMBER: 131:271815
TITLE: Preparation of 2(1H)-quinolinones as serine protease inhibitors for treatment of thrombotic disorders
INVENTOR(S): Dudley, Danette Andrea; Edmunds, Jeremy John
PATENT ASSIGNEE(S): Warner-Lambert Co., USA

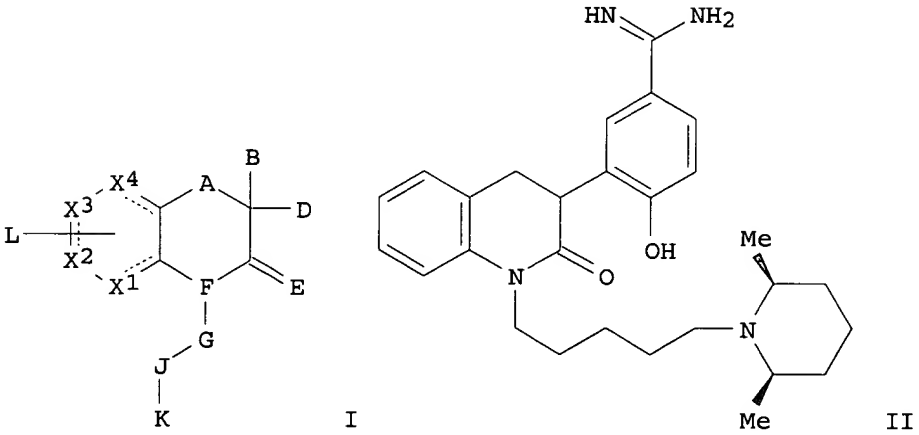
09/ 773,374

SOURCE: PCT Int. Appl., 136 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9950263	A1	19991007	WO 1998-US26709	19981215
W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HR, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2312953	AA	19991007	CA 1998-2312953	19981215
AU 9919184	A1	19991018	AU 1999-19184	19981215
BR 9815786	A	20001121	BR 1998-15786	19981215
EP 1091955	A1	20010418	EP 1998-963966	19981215
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
ZA 9902448	A	20001011	ZA 1999-2448	19990330
NO 2000004696	A	20000920	NO 2000-4696	20000920

PRIORITY APPLN. INFO.: US 1998-80090P P 19980331
WO 1998-US26709 W 19981215

OTHER SOURCE(S): MARPAT 131:271815
GI



I II

AB 2(1H)-Quinolinones (I) [where A = CH2, CH, or C(alkyl); B and D = independently H, (un)substituted (cyclo)alkyl, hetero(cyclo)alkyl, aryl(alkyl), or heterocycle; E = absent or O, S, or NH; F = N, NCH2, or CH2N; G and (un)substituted K = independently absent or (cyclo)alkyl interrupted by 1 or more heteroatoms; J = absent or (un)substituted aryl or heterocycle; L = H, halogen, OH, (un)substituted alkoxy, alkyl, amino, etc.; X1-X4 = independently C or N], which display inhibitory effects on serine proteases such as factor Xa, thrombin and/or factor VIIa, were prepd. For example, 1,5-dibromopentane was added to 4-(benzyloxy)-3-(2-oxo-1,2,3,4-tetrahydro-3-quinolinyl)benzenecarbonitrile (5-step prepn. given) to yield the N-substituted tetrahydroquinolinone. Cis-2,6-dimethylpiperidine was added to the 5-bromopentylquinolinone to

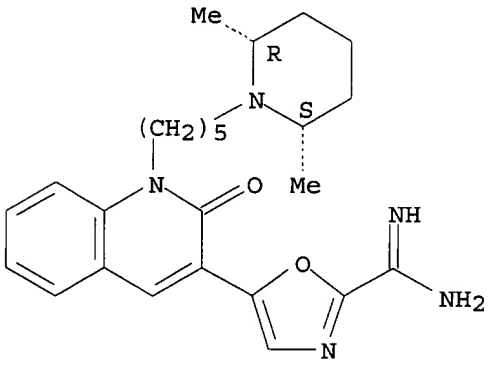
form the piperidinylpentyl deriv. This intermediate was converted to the title quinolinone II.2HCl by treatment with NH2OH.HCl followed by addn. of CF3CO2H and redn. with Pd/C. Typically, the compds. of the invention showed 50% inhibition of factor Xa proteolytic activity on a synthetic substrate in concns. ranging from 50 .mu.M to 1 nM. II demonstrated inhibitory activity in std. assays of thrombin (IC50 = 1.14 .mu.M), trypsin (IC50 = 0.562 .mu.M), and factor Xa (IC50 = 0.02 .mu.M). Compds. of the invention are claimed to be useful in the treatment or prevention of venous and arterial **thrombosis**, pulmonary embolism, myocardial and cerebral **infarction**, restenosis, cancer, **angina**, diabetes, heart failure, and atrial fibrillation in mammals.

IT **245422-39-3P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 2(1H)-quinolinones as serine protease inhibitors for treatment of thrombotic disorders)

RN 245422-39-3 CAPLUS

CN 2-Oxazolecarboximidamide, 5-[1-[5-[(2R,6S)-2,6-dimethyl-1-piperidinyl]pentyl]-1,2-dihydro-2-oxo-3-quinolinyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 18 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:640844 CAPLUS
DOCUMENT NUMBER: 131:271886
TITLE: Preparation of quinoxalinones as serine protease inhibitors for treatment of thrombotic disorders
INVENTOR(S): Dudley, Danette Andrea; Edmunds, Jeremy John
PATENT ASSIGNEE(S): Warner-Lambert Co., USA
SOURCE: PCT Int. Appl., 104 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9950254	A1	19991007	WO 1998-US26704	19981215

W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HR, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG,

KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9919179	A1	19991018	AU 1999-19179		19981215
BR 9815785	A	20001205	BR 1998-15785		19981215
EP 1068190	A1	20010117	EP 1998-963961		19981215
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
ZA 9902447	A	20001010	ZA 1999-2447		19990330
NO 2000004697	A	20000920	NO 2000-4697		20000920
PRIORITY APPLN. INFO.:			US 1998-80042P	P	19980331
			WO 1998-US26704	W	19981215

OTHER SOURCE(S): MARPAT 131:271886
GI

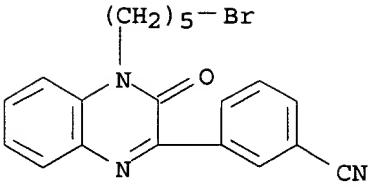
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB 2(1H)-Quinoxalinones (I) [where A = N, N(alkyl)CH2, CH2N(alkyl), NO; B and D = independently H, (un)substituted (cyclo)alkyl, hetero(cyclo)alkyl, aryl(alkyl), or heterocycle; E = absent or O, S, or NH; F = N, NCH2, or CH2N; G and (un)substituted K = independently absent or (cyclo)alkyl interrupted by 1 or more heteroatoms; J = absent or (un)substituted aryl or heterocycle; L = H, halogen, OH, (un)substituted alkoxy, alkyl, amino, etc.; X1-X4 = independently C or N], which display inhibitory effects on serine proteases such as factor Xa, thrombin, trypsin, and/or factor VIIa, were prepd. For example, 1,5-dibromopentane was added to 4-(benzyloxy)-3-(3-oxo-3,4-dihydro-2-quinoxalinyl)benzenecarbonitrile (6-step prepn. given) to yield the N-substituted dihydroquinoxaline. Cis-2,6-dimethylpiperidine was added to the 5-bromopentylquinoxalinone to form the piperidinylpentyl deriv. This intermediate was debenzylated and the nitrile converted to the carboximidamide to form the title quinoxalinone (II).2HCl. Typically, the compds. of the invention showed 50% inhibition of factor Xa proteolytic activity on a synthetic substrate in concns. ranging from 50 .mu.M to 1 nM. II demonstrated inhibitory activity in std. assays of thrombin (IC50 = 2.96 .mu.M), trypsin (IC50 = 2.03 .mu.M), and factor Xa (IC50 = 0.065 .mu.M). At a concn. of 100 .mu.M, II inhibited the catalytic activity of human tissue factor/factor VIIa complex by 16%. In an in vitro assay, II demonstrated human prothrombinase (PTase) complex inhibition with an IC50 of 0.0015 .mu.M. The effects of II on **thrombosis** and hemostasis was studied in a rabbit veno-venous shunt model and in a dog electrolytic injury model of **thrombosis**. At the highest dose, II prolonged a PTT and PT by a 5- and 3.9-fold, resp., for the veno-venous shunt model and by 1.4- and 1.75-fold, resp., for the electrolytic injury model. Compds. of the invention are claimed to be useful in the treatment or prevention of venous and arterial **thrombosis**, pulmonary embolism, myocardial and cerebral **infarction**, restenosis, cancer, **angina**, diabetes, heart failure, and atrial fibrillation in mammals.

IT **245554-84-1P**, 1-(5-Bromopentyl)-3-(3-cyanophenyl)-1,2-dihydro-2-quinoxalinone
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(intermediate; prepn. of 2(1H)-quinolinones as serine protease inhibitors for treatment of thrombotic disorders)

RN 245554-84-1 CAPLUS

CN Benzonitrile, 3-[4-(5-bromopentyl)-3,4-dihydro-3-oxo-2-quinoxalinyl]-(9CI) (CA INDEX NAME)



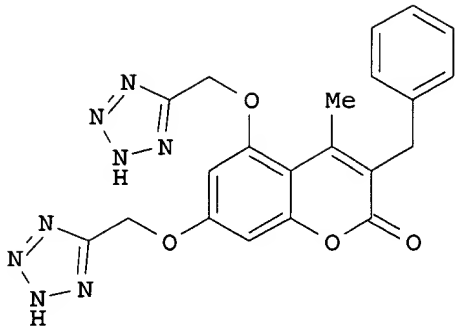
REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 19 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:401691 CAPLUS
DOCUMENT NUMBER: 131:58764
TITLE: A method for the prevention and treatment of stunned myocardium using benzopyranones, quinolinones, and other phospholamban inhibitors
INVENTOR(S): Haikala, Heimo; Kaheinen, Petri; Levijoki, Jouko; Kaivola, Juha; Ovaska, Martti; Pystynen, Jarmo
PATENT ASSIGNEE(S): Orion Corporation, Finland
SOURCE: PCT Int. Appl., 64 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9930696	A1	19990624	WO 1998-FI976	19981211
W: AU, BA, BG, BR, CA, CN, CZ, EE, GE, HR, HU, ID, IL, IS, JP, KP, KR, LT, LV, MK, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, US, UZ, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
ZA 9811180	A	19990609	ZA 1998-11180	19981207
CA 2311932	AA	19990624	CA 1998-2311932	19981211
AU 9915655	A1	19990705	AU 1999-15655	19981211
EP 1039884	A1	20001004	EP 1998-959929	19981211
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 9813549	A	20001010	BR 1998-13549	19981211
JP 2002508314	T2	20020319	JP 2000-538679	19981211

PRIORITY APPLN. INFO.: US 1997-990146 A 19971212
WO 1998-FI976 W 19981211

GI



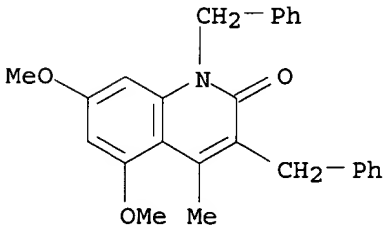
I

AB A method for the prevention and treatment of stunning of the heart subsequent to ischemia-reperfusion is described. The method comprises administering a therapeutically effective amt. of a phospholamban inhibitor to a patient. Phospholamban inhibitors relieve the inhibitory effect of phospholamban on **cardiac** sarcoplasmic reticulum Ca2+-ATPase. Preps. of 24 inhibitors are given, along with results of 3 biol. expts. For instance, acid-catalyzed cyclocondensation of phloroglucinol dihydrate with Et 2-benzylacetoacetate (96%), followed by bis-O-alkylation with ClCH2CN (88%), and cyclization of the nitriles with NaN3 in the presence of NH4Cl (81%), gave title compd. I. This compd., at 100 .mu.M in vitro, gave a 42% stimulation of Ca2+ uptake into **cardiac** vesicles prepd. from guinea pig ventricular myocardium contg. phospholamban, but a 6% inhibition of Ca2+ uptake into fast skeletal muscle vesicles which do not contain it.

IT **219552-06-4P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(intermediate; prepn. of benzopyranones and quinolinones as phospholamban inhibitors for the prevention and treatment of stunned myocardium)

RN 219552-06-4 CAPLUS

CN 2(1H)-Quinolinone, 5,7-dimethoxy-4-methyl-1,3-bis(phenylmethyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 20 OF 61 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1999:81591 CAPLUS

DOCUMENT NUMBER: 130:134202

TITLE: Use of FVIIa or FVIIai for the treatment of adverse conditions related to the FVIIa-mediated intracellular signaling pathway

INVENTOR(S): Kongsbak, Lars; Bergenhem, Niels; Petersen, Lars Christian; Thastrup, Ole; Foster, Don

PATENT ASSIGNEE(S): Novo Nordisk A/S, Den.

SOURCE: PCT Int. Appl., 54 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9903498	A1	19990128	WO 1998-DK280	19980626
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9881016	A1	19990210	AU 1998-81016	19980626
EP 1005361	A1	20000607	EP 1998-930651	19980626
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 2001510168	T2	20010731	JP 2000-502794	19980626
US 6268163	B1	20010731	US 1998-116748	19980716

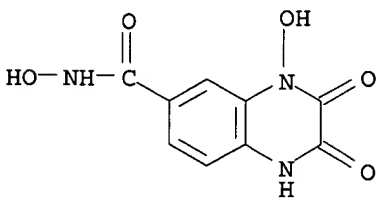
PRIORITY APPLN. INFO.: DK 1997-879 A 19970718
US 1997-52922P P 19970721
WO 1998-DK280 W 19980626

OTHER SOURCE(S): MARPAT 130:134202

AB An intracellular signaling activity of coagulation factor VII (FVII) in cells expressing tissue factor (TF) is described. The invention relates to use of FVIIa or another TF agonist, or FVIIai (FVIIa having at least one modification in its catalytic center) or another TF antagonist for the prepn. of a medicament for modulation of FVIIa-induced activation of the MAPK signaling pathway in a patient. Moreover, the invention relates to a method of treatment, and a method of detecting the activity of compds., in particular drug candidates, that interact with the FVIIa mediated intracellular signaling pathway.

IT **201293-59-6P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(factor VIIa or modified factor VIIa for treatment of adverse conditions related to factor VIIa-mediated intracellular signaling pathway)

RN 201293-59-6 CAPLUS
CN 6-Quinoxalinecarboxamide, 1,2,3,4-tetrahydro-N,4-dihydroxy-2,3-dioxo- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 21 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:42580 CAPLUS
DOCUMENT NUMBER: 130:90514
TITLE: Preparation and use of phospholamban inhibitors for

increasing coronary flow

INVENTOR(S): Pystynen, Jarmo; Haikala, Heimo; Kaheinen, Petri; Kaivola, Juha; Pollesello, Piero; Ulmanen, Ismo; Tenhunen, Jukka; Tilgmann, Carola
PATENT ASSIGNEE(S): Orion Corporation, Finland
SOURCE: PCT Int. Appl., 63 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9900132	A1	19990107	WO 1998-FI559	19980625
W: AU, BA, BG, BR, CA, CN, CZ, EE, FI, GE, HU, ID, IL, IS, JP, KP, KR, LT, LV, MK, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, US, UZ, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
ZA 9805512	A	19990120	ZA 1998-5512	19980624
AU 9879216	A1	19990119	AU 1998-79216	19980625
EP 1001774	A1	20000524	EP 1998-929466	19980625
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 9810335	A	20000905	BR 1998-10335	19980625
JP 2002506457	T2	20020226	JP 1999-505307	19980625

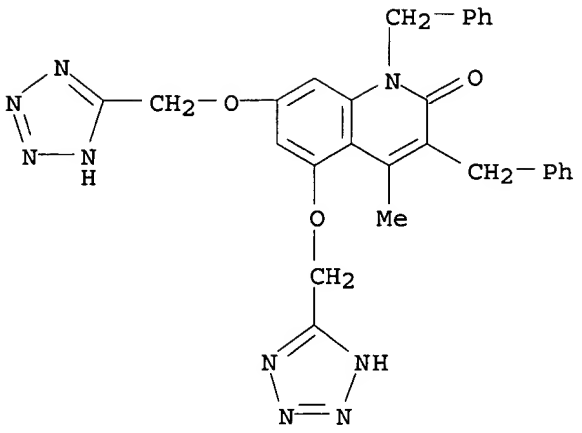
PRIORITY APPLN. INFO.: US 1997-882262 A 19970625
US 1997-937118 A 19970924
WO 1998-FI559 W 19980625

OTHER SOURCE(S): MARPAT 130:90514

AB A method is provided for obtaining direct dilatation of the coronary arteries by administering a therapeutically effective amt. of a phospholamban inhibitor. Compds. which are effective in relieving the inhibitory effects of phospholamban on **cardiac** sarcoplasmic reticulum Ca2+-ATPase are also described. Prepn. and testing of e.g. 3-benzyl-5,7-bis[(1H-tetrazol-5-yl)methoxy]-4-methyl-2H-1-benzopyran-2-one is described.

IT **219552-02-0P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(phospholamban inhibitors, and prepn. thereof, for increasing coronary flow)

RN 219552-02-0 CAPLUS
CN 2(1H)-Quinolinone, 4-methyl-1,3-bis(phenylmethyl)-5,7-bis(1H-tetrazol-5-ylmethoxy)- (9CI) (CA INDEX NAME)



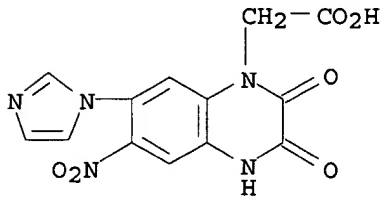
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 22 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:743856 CAPLUS
DOCUMENT NUMBER: 130:105240
TITLE: Neuroprotective efficacy of YM872, an .alpha.-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor antagonist, after permanent middle cerebral artery occlusion in rats
AUTHOR(S): Takahashi, Masayasu; Ni, Jian Wei; Kawasaki-Yatsugi, Sachiko; Toya, Takashi; Ichiki, Chikako; Yatsugi, Shin-Ichi; Koshiya, Kazuo; Shimizu-Sasamata, Masao; Yamaguchi, Tokio
CORPORATE SOURCE: Neuroscience Research, Pharmacology Laboratories, Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co., Ltd., Tsukuba, 305-8585, Japan
SOURCE: J. Pharmacol. Exp. Ther. (1998), 287(2), 559-566
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: Lippencott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The neuroprotective efficacy of YM872, a novel, highly water-sol. .alpha.-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor antagonist, was investigated in rats subjected to permanent occlusion of the left middle cerebral artery. The rats were assessed either histol. or neurol. 24 h or 1 wk after ischemia. YM872 was i.v. infused for either 4 or 24 h at dose rates of 0 to 20 mg/kg/h starting 5 min after ischemia to examine the effect of prolonged treatment. YM872 was then infused at 20 mg/kg/h beginning 0 to 4 h after ischemia to det. the efficacy time window. Addnl., a 20 mg/kg/h dose rate of YM872 was infused for 4 h in single day- or 5-day repetitive-administrations to evaluate long-term benefits of the drug. YM872 significantly reduced **infarct** vol. in both 4- and 24-h treatment groups measured 24 h after ischemia. No difference was obsd. in the degree of protection between length of infusion. Significant neuroprotection was maintained even when drug administration was delayed up to 2 h after ischemia. A single YM872-administration significantly improved neurol. deficit and reduced **infarct** vol. (30%, P < .01) measured 1 wk after ischemia. YM872 treatment did not induce such adverse effects as physiol. changes, serious behavioral abnormalities or nephrotoxicity. These data suggest that the .alpha.-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor plays a crucial role in the progression of neuronal damage in the early phase of ischemia and that YM872 may be useful in treating acute ischemic stroke.

IT **210245-80-0**, YM872

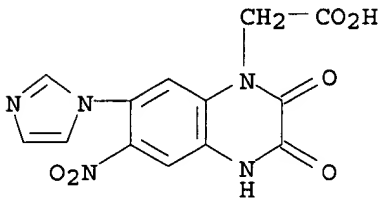
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neuroprotective effect of AMPA receptor antagonist YM872)
RN 210245-80-0 CAPLUS
CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 23 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:691232 CAPLUS
DOCUMENT NUMBER: 130:133986
TITLE: Neuroprotective effect of the novel glutamate AMPA receptor antagonist YM872 assessed with in vivo MR imaging of rat MCA occlusion
AUTHOR(S): Haberg, Asta; Takahashi, Masayasu; Yamaguchi, Tokio; Hjelstuen, Mari; Haraldseth, Olav
CORPORATE SOURCE: RIT, MR-Center, University Hospital, Trondheim, N-7006, Norway
SOURCE: Brain Res. (1998), 811(1,2), 63-70
CODEN: BRREAP; ISSN: 0006-8993
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The neuroprotective effect of post-ischemic treatment with the novel, highly water-sol., glutamate AMPA receptor antagonist YM872 was evaluated by using MR imaging and histopathol. of rats subjected to permanent MCA occlusion. Two treatment groups with continuous i.v. infusion of 20 mg kg-1 h-1 YM872 during either the first 4 h or first 24 h after MCA occlusion, called 4 h YM872 treatment group (n=9) and 24 h YM872 treatment group (n=8) resp., were compared to a control group (n=8). The main end-point was T2 weighted MR imaging and histopathol. 24 h after MCA occlusion. Also the time evolution of the ischemic tissue damage was studied by diffusion weighted MR imaging 4 and 24 h after MCA occlusion. The vol. of ischemic tissue damage as assessed by diffusion weighted MR imaging 4 h after MCA occlusion was significantly smaller in both YM872 treatment groups (99.+-.52 mm3 and 102.+-.44 mm3 compared to 186.+-.72 mm3 in the control group, .+-.S.D. and p=0.008). The **infarct** vol. as assessed by T2 weighted MR imaging 24 h after MCA occlusion was significantly smaller only in the 24 h YM872 treatment group (262.+-.57 mm3 compared to 366.+-.49 mm3 in the control group, .+-.S.D. and p=0.01) while the **infarct** vol. in the 4 h YM872 treatment group (357.+-.88 mm3) was similar to the control group. YM872 treatment significantly reduced the **infarct** vol. 24 h after MCA occlusion when the drug was administered as continuous infusion during the 24-h observation period.
IT **210245-80-0**, YM872
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neuroprotective effect of AMPA receptor antagonist YM872 assessed with in vivo MR imaging of rat MCA occlusion)
RN 210245-80-0 CAPLUS

CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)

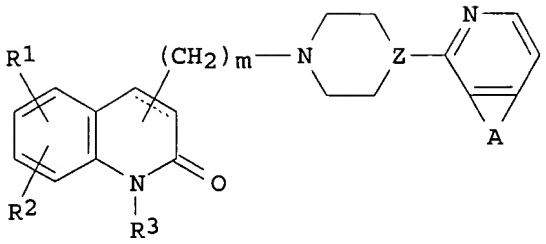


REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

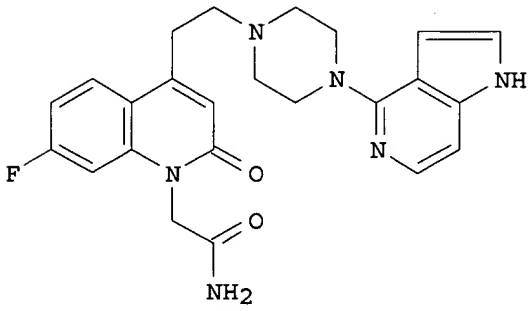
L5 ANSWER 24 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:672552 CAPLUS
DOCUMENT NUMBER: 129:275934
TITLE: Quinolin-2(1H)-one and dihydroquinolin-2(1H)-one derivatives as ligands of 5-HT, 5-HT2 and 5-HT1-like receptors
INVENTOR(S): McCort, Gary; Hoornaert, Christian; Cadilhac, Caroline; Duclos, Olivier; Guilpain, Eric
PATENT ASSIGNEE(S): Synthelabo, Fr.
SOURCE: PCT Int. Appl., 89 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9842712	A1	19981001	WO 1998-FR528	19980317
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
FR 2761071	A1	19980925	FR 1997-3387	19970320
FR 2761071	B1	19991203		
AU 9869239	A1	19981020	AU 1998-69239	19980317
EP 971928	A1	20000119	EP 1998-914928	19980317
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
ZA 9802362	A	19980923	ZA 1998-2362	19980319

PRIORITY APPLN. INFO.: FR 1997-3387 19970320
WO 1998-FR528 19980317
OTHER SOURCE(S): MARPAT 129:275934
GI



I



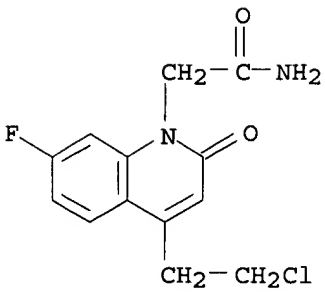
II

AB The invention concerns compds. I [dashed line = single or double bond; major sidechain is in position 3 or 4; Z = N or CH; R1, R2 = H, halo, amino, OH, NO2, cyano, (C1-6) alkyl, (C1-6) alkoxy, CF3, CF3O, COOH, COOR4, CONH2, CONHR4, CONR4R5, SR4, SO2R4, NHCOR4, NHSO2R4, N(R4)2; R3 = H, (C1-4) alkyl, (CH2)pOH, (CH2)pNH2, (CH2)nCOOH, (CH2)nCOOR4, (CH2)nCN, (CH2)n-tetrazolyl, (CH2)nCONH2, (CH2)nCONHOH, (CH2)pSH, (CH2)nSO3H, (CH2)nSO2NH2, (CH2)nSO2NHR4, (CH2)nSO2NR4R5, (CH2)nCONHR4, (CH2)nCONR4R5, (CH2)pNHSO2R4, (CH2)pNHCOR4, (CH2)pOCOR4; R4, R5 = (C1-4) alkyl; m = 2-4; n = 1-4; p = 2-4; A = optional (un)substituted benzo or hetero fusion; with provisos] and salts. The compds. are antagonists of serotoninergic receptors, notably 5-HT2 or 5-HT1-like subtypes. The invention is thereby applicable in therapeutics, particularly for treatment or prevention of cardiovascular pathologies such as ischemias, **angina**, thromboses, atherosclerosis, various hypertensions, and vasospasms. For instance, 4-(2-chloroethyl)-7-fluoro-2-oxo-1,2-dihydroquinoline-1-acetamide (prepd. in 6 steps) was coupled with 4-(piperazin-1-yl)-1H-pyrrolo[3,2-c]pyridine (prepd. in 8 steps) using NaHCO3 and KI in MeCN-DMF mixt. at 70.degree., followed by acidification with HCl in Et2O, to give title compd. II.2HCl in 64% yield. In a test for inhibition of [3H]-spiroperidol specific binding to rat cerebral 5-HT2 receptors in vitro, I had IC50 values of < 1 .mu.M.

IT **214045-59-7P**, 4-(2-Chloroethyl)-7-fluoro-2-oxo-1,2-dihydroquinoline-1-acetamide
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(intermediate; prepn. of piperazinylalkyl quinolinone and dihydroquinolinone derivs. as serotoninergic antagonists)

RN 214045-59-7 CAPLUS

CN 1(2H)-Quinolineacetamide, 4-(2-chloroethyl)-7-fluoro-2-oxo- (9CI) (CA INDEX NAME)



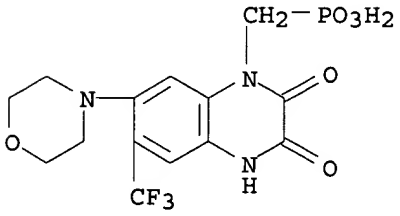
L5 ANSWER 25 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:591413 CAPLUS
DOCUMENT NUMBER: 129:310816
TITLE: ZK200775: a phosphonate quinoxalinedione AMPA antagonist for neuroprotection in stroke and trauma
AUTHOR(S): Turski, Lechoslaw; Huth, Andreas; Sheardown, Malcolm; McDonald, Fiona; Neuhaus, Roland; Schneider, Herbert H.; Dirnagl, Ulrich; Wiegand, Frank; Jacobsen, Poul; Ottow, Eckhard
CORPORATE SOURCE: Research Laboratories of Schering AG, Berlin, D-13342, Germany
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1998), 95(18), 10960-10965
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Stroke and head trauma are worldwide public health problems and leading causes of death and disability in humans, yet, no adequate neuroprotective treatment is available for therapy. Glutamate antagonists are considered major drug candidates for neuroprotection in stroke and trauma. However, N-methyl-D-aspartate antagonists failed clin. trials because of unacceptable side effects and short therapeutic time window. .alpha.-Amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) antagonists derived from the quinoxalinedione scaffold cannot be used in humans because of their insoly. and resulting renal toxicity. Therefore, achieving water soly. of quinoxalinediones without loss of selectivity and potency profiles becomes a major challenge for medicinal chem. One of the major tenets in the chem. of glutamate antagonists is that the incorporation of phosphonate into the glutamate framework results in preferential N-methyl-D-aspartate antagonism. Therefore, synthesis of phosphonate derivs. of quinoxalinediones was not pursued because of a predicted loss of their selectivity toward AMPA. Here, the authors report that introduction of a methylphosphonate group into the quinoxalinedione skeleton leaves potency as AMPA antagonists and selectivity for the AMPA receptor unchanged and dramatically improves soly. One such novel phosphonate quinoxalinedione deriv. and competitive AMPA antagonist ZK200775 exhibited a surprisingly long therapeutic time window of >4 h after permanent occlusion of the middle cerebral artery in rats and was devoid of renal toxicity. Furthermore, delayed treatment with ZK200775 commencing 2 h after onset of reperfusion in transient middle cerebral artery occlusion resulted in a dramatic redn. of the **infarct** size. ZK200775 alleviated also both cortical and hippocampal damage induced by head trauma in the rat. These observations suggest that phosphonate quinoxalinedione-based AMPA antagonists may offer new prospects for treatment of stroke and trauma in humans.

IT **161605-73-8**, ZK 200775
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process);

USES (Uses)
(ZK200775 as phosphonate quinoxalinedione AMPA antagonist for neuroprotection in stroke and trauma in relation to binding to AMPA receptors and structure and pharmacol.)

RN 161605-73-8 CAPLUS
CN Phosphonic acid, [[3,4-dihydro-7-(4-morpholinyl)-2,3-dioxo-6-(trifluoromethyl)-1(2H)-quinoxalinyl]methyl]- (9CI) (CA INDEX NAME)

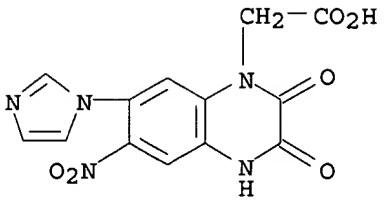


L5 ANSWER 26 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:343162 CAPLUS
DOCUMENT NUMBER: 129:117773
TITLE: A novel AMPA receptor antagonist, YM872, reduces **infarct** size after middle cerebral artery occlusion in rats
AUTHOR(S): Kawasaki-Yatsugi, Sachiko; Yatsugi, Shin-ichi; Takahashi, Masayasu; Toya, Takashi; Ichiki, Chikako; Shimizu-Sasamata, Masao; Yamaguchi, Tokio; Minematsu, Kazuo
CORPORATE SOURCE: Pharmacological Laboratory, Neuroscience Research, Institute for Drug Discovery Research, Yamanouchi Pharmaceutical, Tsukuba, Japan
SOURCE: Brain Res. (1998), 793(1,2), 39-46
CODEN: BRREAP; ISSN: 0006-8993
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The neuroprotective effect of YM-872 ([2.3-dioxo-7-(1H-imidazol-1-yl)-6-nitro-1,2,3,4-tetrahydro-1-quinoxalinyl]acetic acid monohydrate), a novel .alpha.-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptor antagonist with improved water soly., was examd. in the rat focal cerebral ischemia model. Rats were subjected to permanent middle cerebral artery (MCA) occlusion using the intraluminal suture occlusion method for 24 h. YM-872 was infused i.v. for 4 h (20 and 40 mg/kg/h) or 24 h (10 and 20 mg/kg/h), starting 5 min after the MCA occlusion, to investigate the effect of prolonged YM-872 treatment on **infarction** vol. In the 4 h infusion study, YM-872 reduced the cortical **infarction** vol. by 48% at a dose of 40 mg/kg/h. YM-872 did not reduce the **infarction** size at 20 mg/kg/h for 4 h. In the 24-h infusion study, YM-872 markedly reduced the cortical **infarction** vol. by 62% even at 20 mg/kg/h. Thus, the neuroprotective effects of YM-872 are enhanced by extending the duration of treatment. YM-872 is applicable to investigate the role of AMPA receptors in ischemic models without concern about nephrotoxicity and could be useful in the treatment of human stroke.

IT **210245-80-0**, YM 872
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(YM-872 antagonist of AMPA receptors reduces **infarction** size after middle cerebral artery occlusion in rats)

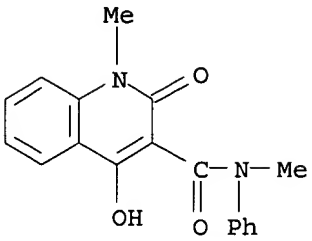
RN 210245-80-0 CAPLUS
CN 1(2H)-Quinoxalineacetic acid, 3,4-dihydro-7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo- (9CI) (CA INDEX NAME)



L5 ANSWER 27 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:234288 CAPLUS
DOCUMENT NUMBER: 128:317073
TITLE: The effects of leflunomide and cyclosporin A on rejection of **cardiac** allografts in the rat
AUTHOR(S): Ostraat, O.; Qi, Z. -Q.; Tufveson, G.; Hedlund, G.; Ekberg, H.
CORPORATE SOURCE: Department of Vascular and Renal Diseases, Lund University, Malmo, S-205 02, Swed.
SOURCE: Scand. J. Immunol. (1998), 47(3), 236-242
CODEN: SJIMAX; ISSN: 0300-9475
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Leflunomide is a new low mol. wt. immunosuppressive drug which inhibits the enzymes dehydroorotate-dehydrogenase and protein tyrosine kinase, both of which are important components in the immune response. As the mechanisms of action of leflunomide and cyclosporin A (CsA) are different, we postulated a synergistic effect of the two drugs and tested graft survival following leflunomide administration alone or in combination with CsA in a rat **cardiac** transplantation model. Low- and high-responder rat strain combinations were used in parallel and the expts. were performed both with and without challenge with Linomide, an immunomodulator which promotes graft rejection in this model. In the low-responder rat strain combination (Piebald Virol Glaxo graft to Dark Agouti recipient; PVG to DA), graft survival appeared to be a dichotomous variable, being characterized by tolerance or early rejection. Leflunomide (10 or 5 mg/kg) given for 10 days induced tolerance and CsA did likewise; the addn. of Linomide abolished the immunosuppressive effect of leflunomide but not that of CsA. In the high-responder combination (DA to PVG), no tolerance was seen and graft survival was moderately prolonged both after leflunomide and after CsA treatment; the addn. of Linomide to CsA or to leflunomide (5 mg/kg) abolished the immunosuppressive effect of the drugs. However, when CsA-Linomide or leflunomide-Linomide were supplemented with the second immunosuppressive drug, leflunomide or CsA resp., graft survival was significantly prolonged ($P < 0.001$ in both cases). This suggests leflunomide and CsA have additive potential.

IT **84088-42-6**, Linomide
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(leflunomide and cyclosporin A effect on **cardiac** allograft rejection)
RN 84088-42-6 CAPLUS
CN 3-Quinolinecarboxamide, 1,2-dihydro-4-hydroxy-N,1-dimethyl-2-oxo-N-phenyl- (9CI) (CA INDEX NAME)

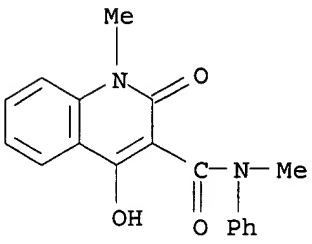


L5 ANSWER 28 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:771973 CAPLUS
DOCUMENT NUMBER: 128:33546
TITLE: Single dose anti-CD4 monoclonal antibody for induction of tolerance to **cardiac** allograft in high- and low-responder rat strain combinations
AUTHOR(S): Qi, Zhongquan; Riesbeck, Kristian; Ostraat, Oyvind; Tufveson, Gunnar; Ekberg, Henrik
CORPORATE SOURCE: Department of Experimental Research, University Hospital, Lund University, Malmo, 205 02, Swed.
SOURCE: Transplant Immunol. (1997), 5(3), 204-211
CODEN: TRIME2; ISSN: 0966-3274
PUBLISHER: Arnold, Hodder Headline PLC
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Repeated administration of monoclonal antibodies (mAb) directed against the CD4 lymphocyte receptor may induce specific, long-lasting unresponsiveness to fully MHC-mismatched **cardiac** allografts in rats without addnl. immunosuppression. The authors assessed the effect of a single dose of murine anti-rat depleting anti-CD4 mAb (OX-38) on allograft survival in high- and low-responder rat strain combinations. Isogenic strains of DA (RT1avl), PVG (RT1c), AUG (RT1c), and WF (RT1u) rats were used. Recipients in antibody treated groups were given one dose of 5 mg/kg OX-38 mAb on the day of transplant, a dose which was shown to effectively deplete (or block) circulating CD4+ T cells. Other groups were treated for 10 days with cyclosporin A (CsA) and/or Linomide, a novel immunomodulator, which is the first compd. able to fully eliminate the effect of CsA in the rat **cardiac** allograft model. The DA strain was identified as a low-responder to the allogeneic haplotype RT1c (PVG or AUG), but not to RT1u (WF), and developed true tolerance following RT1c grafting and OX-38 or low-dose CsA (5 mg/kg) induction, as verified by the response to retransplantation of a graft from the same donor strain or a third-party challenge. PVG recipients of DA grafts were characterized by high response and only modest (OX-38; median 9.5 days) or moderate (CsA; 23.5 days) prolongation of graft survival. Contrasting graft survival results were obtained in the low-responder combination, either very early rejection (at 10 days) or permanent graft survival (>100 days). Linomide challenge affected CsA treatment in the high-responder combination but not tolerance induction in the low-responder combination, or the effect of OX-38. Thus, in rat heart transplantation a single-dose anti-CD4 mAb therapy may induce permanent donor-specific unresponsiveness in a low-responder strain combination, and anti-CD4 mAb seems to be unique among immunosuppressive agents while being resistant to challenge by Linomide.

IT **84088-42-6**, Linomide
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(single dose anti-CD4 monoclonal antibody for induction of tolerance to **cardiac** allograft in high- and low-responder rat strain combinations)

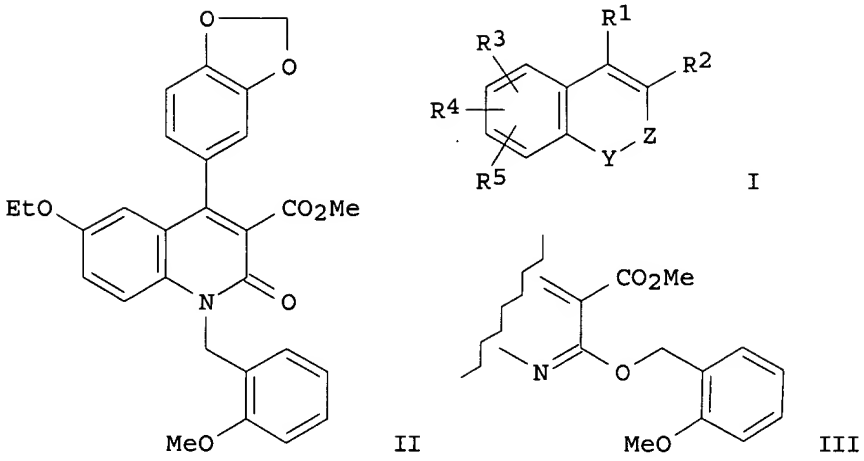
RN 84088-42-6 CAPLUS
CN 3-Quinolinecarboxamide, 1,2-dihydro-4-hydroxy-N,1-dimethyl-2-oxo-N-phenyl- (9CI) (CA INDEX NAME)



L5 ANSWER 29 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:220525 CAPLUS
DOCUMENT NUMBER: 126:212055
TITLE: Quinoline derivatives useful as endothelin receptor antagonists
INVENTOR(S): Mederski, Werner; Osswald, Mathias; Dorsch, Dieter; Wilm, Claudia; Schmitges, Claus J.; Christadler, Maria
PATENT ASSIGNEE(S): Merck Patent Gmbh, Germany
SOURCE: Eur. Pat. Appl., 73 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 757039	A1	19970205	EP 1996-112347	19960731
R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
DE 19528418	A1	19970206	DE 1995-19528418	19950802
AU 9660792	A1	19970206	AU 1996-60792	19960729
AU 705959	B2	19990603		
CA 2182469	AA	19970203	CA 1996-2182469	19960731
NO 9603213	A	19970203	NO 1996-3213	19960801
US 5731321	A	19980324	US 1996-691148	19960801
BR 9603252	A	19980428	BR 1996-3252	19960801
JP 09040649	A2	19970210	JP 1996-219113	19960802

PRIORITY APPLN. INFO.: DE 1995-19528418 19950802
OTHER SOURCE(S): MARPAT 126:212055
GI

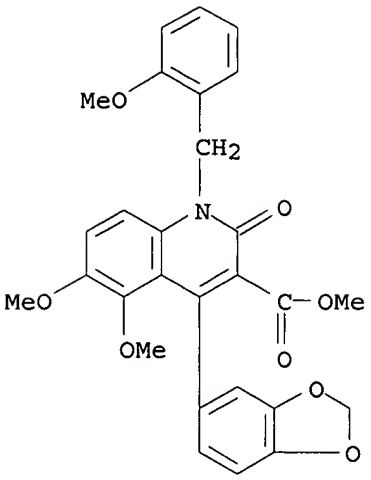


AB Title compds. I and their salts are claimed [wherein YZ = NR7CO, N:C(OR7), N:CR8; R1 = Ar; R2 = CO2R6, (CH2)nCO2R6, cyano, 1H-tetrazol-5-yl, CONHSO2Ar; R3, R4, R5 = R6, OR6, SOmR6, halo, NO2, NR6R6', NHCOR6, NHSO2R6, OCOR6, COR6, CO2R6, cyano; or R3R4 = O(CH2)nO; R6, R6' = H, alkyl, CH2Ph, Ph; R7 = (CH2)nAr; R8 = Ar, OAr; Ar = (un)substituted Ph, naphthyl, certain heterocycle-fused Ph groups; m = 0-2; n = 1-3]. I have a high affinity toward endothelin receptor subtypes ETA and ETB (no data), and are useful for treatment of a wide variety of endothelin-related disorders such as hypertension. A large no. of I are listed as examples, some with phys. data and/or synthetic methods. For instance, reaction of 3,4-methylenedioxybenzaldehyde with lithiated p-EtOC6H4NH-Boc, followed by oxidn. of the resulting alc. and removal of the Boc protecting group, gave 1-amino-2-(3,4-methylenedioxybenzoyl)-4-ethoxybenzene. The latter was cyclocondensed with ClCOCH2CO2Me to give a 2-oxoquinoline deriv., which underwent mixed N- and O-alkylation by 2-MeOC6H4CH2Cl and K2CO3 to give title compds. II and III.

IT **188001-42-5P**
RL: BAC (Biological activity or effector, except adverse); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of quinoline derivs. as endothelin receptor antagonists)

RN 188001-42-5 CAPLUS

CN 3-Quinolinecarboxylic acid, 4-(1,3-benzodioxol-5-yl)-1,2-dihydro-5,6-dimethoxy-1-[(2-methoxyphenyl)methyl]-2-oxo-, methyl ester (9CI) (CA INDEX NAME)



L5 ANSWER 30 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:657483 CAPLUS
DOCUMENT NUMBER: 125:292564
TITLE: Moderate additive immunosuppressive effect of thalidomide combined with cyclosporin A in rat **cardiac** transplantation
AUTHOR(S): Oestraat, Oe; Qi, Zhongquan; Gannedahl, Goeran; Tufveson, Gunnar; Ekberg, Henrik
CORPORATE SOURCE: Department Vascular and Renal Diseases, Lund University, Malmoe, 205 02, Swed.
SOURCE: Transplant Immunol. (1996), 4(3), 241-246
CODEN: TRIME2; ISSN: 0966-3274
DOCUMENT TYPE: Journal
LANGUAGE: English

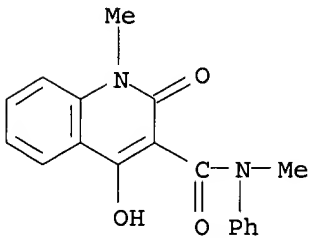
AB Thalidomide is an immunomodulating agent shown to prolong graft survival in exptl. skin, renal, **cardiac** and bone marrow transplantation. The main purpose of the present study was to investigate the possible additive effect of combining thalidomide with cyclosporin A (CyA). Members of our group have previously created a basis for such studies by demonstrating the ability of Linomide to abolish the effect of CyA. The addnl. effect of combined treatment with a second drug is thereby more readily evaluated, compared with using subtherapeutic dose levels to induce early rejection. **Cardiac** grafting was performed in three rat strain combinations (BN to WF, DA to Lew, and BN to Lew). Rats were given no treatment, or thalidomide, CyA and/or Linomide in single, double or triple drug therapy. Except for a consistent beneficial effect of CyA as single drug treatment, graft survival varied depending on the rat strain combination used. In the DA to Lew combination, the expected effects of Linomide were seen, and thalidomide was shown to prolong graft survival significantly ($P = 0.004$) when added to CyA and Linomide. However, there was no effect of thalidomide when given alone. In WF recipients of BN hearts, thalidomide tended to prolong graft survival ($P = 0.07$), and surprisingly Linomide manifested a marked immunosuppressive effect ($P = 0.0002$) and did not counteract the effect of CyA. When transplanting BN grafts to Lew recipients, Linomide reduced significantly but did not abolish completely the effect of CyA. Neither Linomide nor thalidomide had any beneficial impact on graft survival on their own. To sum up, thalidomide was shown to have a minimal or moderate immunosuppressive effect additive to that of CyA. The effects of the two immunomodulating drugs, thalidomide and Linomide, varied depending on the rat strain combination used, and were similar with respect to prolongation of graft survival when used as single drug treatment in BN to WF grafting,

a fact which may indicate them to have a similar mechanism of action, both having been shown to exert similar effects on levels of tumor necrosis factor .alpha..

IT **84088-42-6**, Linomide
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(moderate additive immunosuppressive effect of thalidomide combined with cyclosporin A in rat **cardiac** transplantation)

RN 84088-42-6 CAPLUS

CN 3-Quinolinecarboxamide, 1,2-dihydro-4-hydroxy-N,1-dimethyl-2-oxo-N-phenyl- (9CI) (CA INDEX NAME)



L5 ANSWER 31 OF 61 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1996:590908 CAPLUS

DOCUMENT NUMBER: 125:293037

TITLE: Sigma receptor agonist disturbance-of-consciousness improving agents, their prepn., and pharmaceutical compositions containing them

INVENTOR(S): Oshiro, Yasuo; Tanaka, Tatsuyoshi; Kikuchi, Tetsuro; Tottori, Katsura

PATENT ASSIGNEE(S): Otsuka Pharmaceutical Co., Ltd., Japan

SOURCE: U.S., 23 pp. Cont.-in-part of U.S. Ser. No. 82, 522.
CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5556857	A	19960917	US 1993-92060	19930716
JP 06040946	A2	19940215	JP 1992-189785	19920717
JP 08019002	B4	19960228		
US 5656633	A	19970812	US 1995-465579	19950605

PRIORITY APPLN. INFO.:

JP 1991-102391	19910508
US 1992-878515	19920505
JP 1992-189785	19920717
US 1993-82522	19930625

OTHER SOURCE(S): MARPAT 125:293037

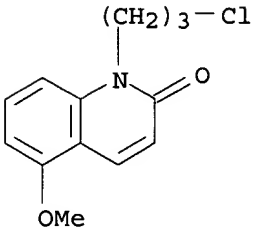
AB A disturbance-of-consciousness improving agent is disclosed which is a highly effective and quick remedy and which can be administered orally. The disturbance-of-consciousness improving agent of the invention contains a sigma receptor agonist compd. as an active ingredient. Prepn. of compds. of the invention is included, as are formulations and sigma receptor binding affinities.

IT **145969-96-6P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(sigma receptor agonist disturbance-of-consciousness improving agent prepn., pharmaceutical compns., and receptor binding affinities)

RN 145969-96-6 CAPLUS

09/ 773,374

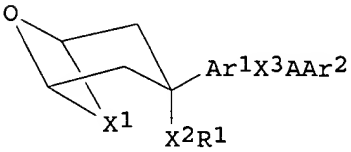
CN 2(1H)-Quinolinone, 1-(3-chloropropyl)-5-methoxy- (9CI) (CA INDEX NAME)



L5 ANSWER 32 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:812768 CAPLUS
DOCUMENT NUMBER: 123:228171
TITLE: Preparation of aryloxabicyclooctanes as inhibitors of leukotriene biosynthesis
INVENTOR(S): Friesen, Richard W.; Girard, Yves; Dube, Daniel
PATENT ASSIGNEE(S): Merck Frosst Canada Inc., Can.
SOURCE: PCT Int. Appl., 69 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9503309	A1	19950202	WO 1994-CA389	19940715
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, FI, GE, HU, JP, KE, KG, KR, KZ, LK, LT, LV, MD, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, TT, UA, US, UZ				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5459271	A	19951017	US 1993-94814	19930720
AU 9472613	A1	19950220	AU 1994-72613	19940715

PRIORITY APPLN. INFO.: US 1993-94814 19930720
WO 1994-CA389 19940715
OTHER SOURCE(S): MARPAT 123:228171
GI



I

AB Title compds. [I; Ar1 = X4(R2)2; X4 = 5-membered arom. ring contg. 1 O or S and in which 0-2 c atoms are replaced by N, 6-membered ring wherein 0-3 C atoms are replaced by N, 2- or 4-pyranone, 2- or 4-pyridinone; Ar2 = X5(R3)2; X5 = 9- or 10-membered bicyclic heterocyclyl contg. 1-2 N and optionally a further N, O, or S; Ar3 = X6(R4)2; X6 = 5-membered arom. ring contg. 1 O, S, or N and in which 0-3 C atoms are replaced by N, 6-membered ring in which 0-3 C atoms are replaced by N, 2- or 4-pyranone, 2- or 4-pyridinone 8-, 9-, or 10-membered arom. ring wherein 0-2 C atoms are relaced by O, S and 0-3 C atoms are replaced by N; A = bond, [C(R5)2]n; X1 = OCH2, CH2CH2, CH:CH; X2 = O, S, bond; X3 = O, S, SO, SO2; R1 = H, alkyl,

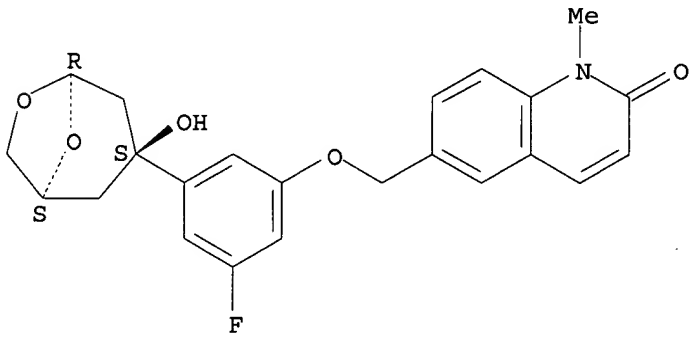
alkoxycarbonyl; R2, R4 = H, alkyl, alkoxy, alkylthio, cyano, CF3, halo; R3 = R2, oxo, thioxo, hydroxyalkyl, alkoxyalkyl, alkylthioalkyl, NO2, N3, etc.; R5 = H, alkyl; CR5R5 = 3- to 8- membered ring], were prepd. as leukotriene biosynthesis inhibitors (no data). I are useful as antiasthmatic, antiallergic, antiinflammatory, and cytoprotective agents. They are also useful in treating **angina**, cerebral spasm, glomerular nephritis, hepatitis, endotoxemia, uveitis and allograft rejection and in preventing the formation of atherosclerotic plaques. Thus, [1S,5R]-1,2-dihydro-1-methyl-6-[5-[3-(3.alpha.-hydroxy-6,8-dioxabicyclo[3.2.1]octyl)]-3-fluorophenoxymethyl]quinolin-2-one was prepd. from 1,6-anhydro-.beta.-D-glucose via 2,4-di-O-p-toluenesulfonyl-1,6-anhydro-.beta.-D-glucose, [1S,3S,5R]-6,8-dioxabicyclo[3.2.1]octan-3-ol, [1S,5R]-6,8-dioxabicyclo[3.2.1]octan-3-one, [1S,5R]-O-benzyl-5-[3-(3.alpha.-hydroxy-6,8-dioxabicyclo[3.2.1]octyl)]-3-fluorophenol, and [1S,5R]-5-[3-(3.alpha.-hydroxy-6,8-dioxabicyclo[3.2.1]octyl)]-3-fluorophenol.

IT **168153-88-6P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of aryloxabicyclooctanes as inhibitors of leukotriene biosynthesis)

RN 168153-88-6 CAPLUS

CN .beta.-D-threo-Hexopyranose, 1,6-anhydro-2,4-dideoxy-3-C-[3-[(1,2-dihydro-1-methyl-2-oxo-6-quinolinyl)methoxy]-5-fluorophenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

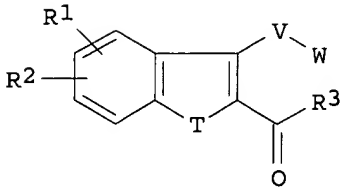


L5 ANSWER 33 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:382651 CAPLUS
DOCUMENT NUMBER: 122:160466
TITLE: Benzofuranyl- and -thienylalkanecarboxylic acid derivatives useful as antiinflammatories
INVENTOR(S): Fischer, Ruediger; Braeunlich, Gabriele; Mohrs, Klaus-Helmut; Hanko, Rudof; Butler-Ransohoff, John-Edward; Es-Sayed, Mazen; Sturton, Graham; Tudhope, Steve; Abram, Trevor; Mcdonald-Gibson, Wendy J.
PATENT ASSIGNEE(S): Bayer A.-G., Germany
SOURCE: Eur. Pat. Appl., 79 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

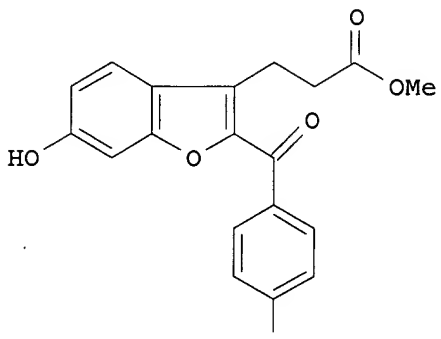
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

EP 623607	A1	19941109	EP 1994-106320	19940422	
EP 623607	B1	19980715			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE					
AU 9460558	A1	19941110	AU 1994-60558	19940419	
AU 678814	B2	19970612			
AT 168373	E	19980815	AT 1994-106320	19940422	
ES 2118283	T3	19980916	ES 1994-106320	19940422	
US 5504213	A	19960402	US 1994-236796	19940429	
JP 06329652	A2	19941129	JP 1994-115923	19940502	
CA 2122788	AA	19941107	CA 1994-2122788	19940503	
FI 9402049	A	19941107	FI 1994-2049	19940504	
NO 9401662	A	19941107	NO 1994-1662	19940505	
ZA 9403100	A	19950109	ZA 1994-3100	19940505	
RU 2125564	C1	19990127	RU 1994-15838	19940505	
CN 1097749	A	19950125	CN 1994-104909	19940506	
HU 67847	A2	19950529	HU 1994-1415	19940506	

PRIORITY APPLN. INFO.: GB 1993-9324 A 19930506
OTHER SOURCE(S): MARPAT 122:160466
GI



I

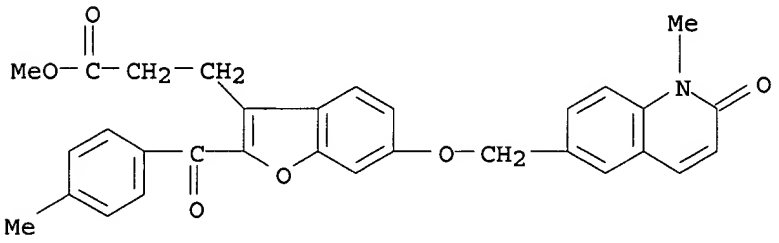


II

AB Title compds. I [R1, R2 = H, halo, CO2H, cyano, NO2, CF3, (un)substituted OH, SH, or NH2; R3 = mono- to trisubstituted Ph; T = O, S; V = straight or branched C2-8 alkylene or alkenylene; W = cyano, tetrazolyl, CO2H or certain esters or amides, PO3H2 or certain esters, 4,4-dimethyl-2-oxazolin-2-yl] are prepd. as antiinflammatories. I inhibit prodn. of superoxide by polymorphonuclear leukocytes (PMN), mediated by elevation of cellular cAMP due to inhibition of type IV phosphodiesterase. Synthetic methods include cyclization of hydroxyacetophenones and related compds., and Wittig reaction of benzofuranyl aldehydes. For example, the diphenolic keto ester 2,4-(HO)2C6H3COCH2CH2CO2Me underwent tetrahydropyranylation of the 4-OH group (56%), cyclocondensation with 4-BrC6H4COCH2Br using K2CO3 in refluxing acetone (65.1%), and removal of the tetrahydropyranyl protecting group with p-MeC6H4SO3H in MeOH (86%), to give title compd. II (E = Br). Incubation of PMN in vitro with the analogously prepd. II (E = Cl) at 1 .mu.M increased cAMP to 394% of control. At 25 mg/kg orally, II (E = Cl) gave 46% inhibition of FMLP-induced skin edema in guinea pigs. Approx. 290 I (T = O) were prepd.

IT **161222-83-9P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of benzofuranyl- and benzothienylalkanecarboxylates as antiinflammatories)

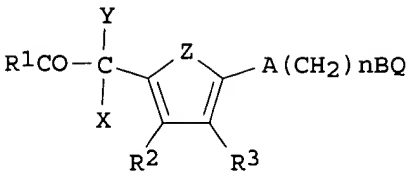
RN 161222-83-9 CAPLUS
CN 3-Benzofuranpropanoic acid, 6-[(1,2-dihydro-1-methyl-2-oxo-6-quinolinyl)methoxy]-2-(4-methylbenzoyl)-, methyl ester (9CI) (CA INDEX NAME)



L5 ANSWER 34 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:277045 CAPLUS
DOCUMENT NUMBER: 122:46487
TITLE: CAT-1 inhibitors, their synthesis, pharmaceutical compositions, and methods of use
INVENTOR(S): Guthrie, Robert W.; Mullin, John G., Jr.; Kachensky, David F.; Kierstead, Richard W.; Tilley, Jefferson W.; Heathers, Guy P.; Higgins, Alan J.; Lemahieu, Ronald A.
PATENT ASSIGNEE(S): Hoffman-La Roche Inc., USA
SOURCE: U.S., 85 pp. Cont.-in-part of U.S. Ser. No. 698, 014, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5344843	A	19940906	US 1992-850620	19920313
RU 2059603	C1	19960510	RU 1992-5011784	19920131
EP 512352	A2	19921111	EP 1992-107135	19920427
EP 512352	A3	19930310		
EP 512352	B1	19960327		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, MC, NL, PT, SE				
AT 136018	E	19960415	AT 1992-107135	19920427
AU 9216003	A1	19921112	AU 1992-16003	19920504
AU 653398	B2	19940929		
CA 2068076	AA	19921110	CA 1992-2068076	19920506
ZA 9203279	A	19930127	ZA 1992-3279	19920506
NO 9201840	A	19921110	NO 1992-1840	19920508
HU 63602	A2	19930928	HU 1992-1538	19920508
JP 05279353	A2	19931026	JP 1992-143375	19920508
JP 07107060	B4	19951115		
RO 109938	B1	19950728	RO 1992-622	19920508
BR 9201769	A	19921229	BR 1992-1769	19920511

PRIORITY APPLN. INFO.: US 1991-698014 B2 19910509
US 1992-850620 A 19920313
OTHER SOURCE(S): MARPAT 122:46487
GI



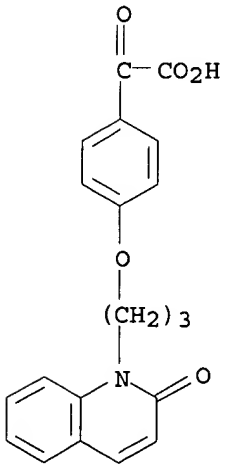
I

AB The invention relates to compds. I (R1 = OH; R2, R3 = H, alkyl, aryl, alkoxy, etc.; X, Y together = O, or one is amino and other is H; Z = S, CR2=CR2'; A = bond, O, S, SO, CHCH, etc.; B = bond, O, S, SO, etc.; Q = Ph, cyclohexyl, pyridinyl, etc.; n = 1-6) and their pharmaceutically acceptable salts, and when appropriate, enantiomers, racemates, diastereomers or mixts. thereof or geometric isomer or mixts. thereof, and pharmaceutically acceptable salts thereof. The compds. inhibit carnitine acyltransferase 1 (CAT-1) and are therefore useful in the prevention of injury to ischemic tissue, and can limit **infarct** size, improve **cardiac** function and prevent arrhythmias during and following a myocardial **infarction**. 5-[[2-(2-Naphthalenyloxy)ethyl]oxy]-.alpha.-oxo-2-thiopheneacetic acid (prepn. given) inhibited CAT-1 with an IC50 = 0.05 .mu.M. Tablet and capsule formulations contg. 4-[2-(2-naphthyloxy)ethoxy]-.alpha.-oxobenzeneacetic acid are presented.

IT **145795-79-5P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis and pharmaceutical compns. and use of carnitine acyltransferase inhibitor compds.)

RN 145795-79-5 CAPLUS

CN Benzeneacetic acid, .alpha.-oxo-4-[3-(2-oxo-1(2H)-quinolinyl)propoxy]- (9CI) (CA INDEX NAME)



L5 ANSWER 35 OF 61 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1994:686599 CAPLUS

DOCUMENT NUMBER: 121:286599

TITLE: Suspension of solid lipid particles as carrier for bioactive agents

INVENTOR(S): Westesen, Kirsten; Siekmann, Britta

PATENT ASSIGNEE(S): Pharmacia AB, Swed.

SOURCE: PCT Int. Appl., 78 pp.
CODEN: PIXXD2

09/ 773,374

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9420072	A1	19940915	WO 1994-SE185	19940304
W: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, UZ, VN				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2113795	AA	19950720	CA 1994-2113795	19940119
AU 9462253	A1	19940926	AU 1994-62253	19940304
AU 676279	B2	19970306		
EP 687172	A1	19951220	EP 1994-909393	19940304
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 08507515	T2	19960813	JP 1994-519887	19940304
FI 9504143	A	19951019	FI 1995-4143	19950904
NO 9503461	A	19951106	NO 1995-3461	19950904

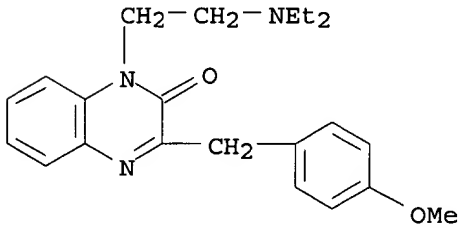
PRIORITY APPLN. INFO.: US 1993-27501 A 19930305
WO 1994-SE185 W 19940304

AB Suspensions of colloidal solid lipid particles (SLPs) of predominantly anisometrical shape, as well as suspensions or the lyophilizates thereof are prepd. and used as delivery systems for the parenteral administration of poorly water-sol. bioactive substances, particularly drugs and vaccines, cosmetics, food and agricultural products. Thus, 0.96 g lecithin and 60 mg lidocaine (I) were dispersed in 4.0 g melted tripalmitate; then 35 mL of heated aq. phase contg. 320 mg Na glycocholate, 0.9 g glycerol and 4 mg thiomersal was added to the melt and sonicated and homogenized to obtain a dispersion of I-loaded SLPs with a mean particle size of 90.4 nm.

IT **23465-76-1**, Caroverine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(suspension of solid lipid particles as carrier for bioactive agents)

RN 23465-76-1 CAPLUS

CN 2(1H)-Quinoxalinone, 1-[2-(diethylamino)ethyl]-3-[(4-methoxyphenyl)methyl]-(9CI) (CA INDEX NAME)



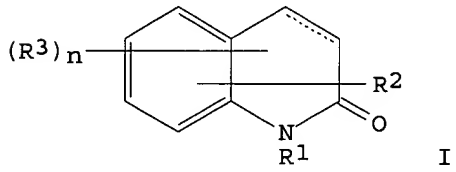
L5 ANSWER 36 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:298482 CAPLUS
DOCUMENT NUMBER: 120:298482
TITLE: Carbostyril derivatives and salts thereof, anti-arrhythmic agents containing them, and their preparation
INVENTOR(S): Tabusa, Fujio; Nagami, Kazuyoshi; Tsutsui, Hironori
PATENT ASSIGNEE(S): Yoshinari Higuchi, Japan
SOURCE: Pat. Specif. (Aust.), 148 pp.
CODEN: ALXXAP
DOCUMENT TYPE: Patent

09/ 773,374

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
AU 639529	B2	19930729	AU 1991-70939	19910211
AU 9170939	A1	19910509		

OTHER SOURCE(S): MARPAT 120:298482
GI

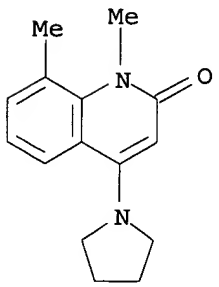


I

AB Carbostyrils and dihydro derivs. I [R1 = H, alkyl, alkenyl, alkynyl, phenylalkyl, carboxyalkyl, phenylalkoxyalkyl, amidoalkyl, satd. heterocyclylcarbonylalkyl; R2 = N3, azidocarbonyl, phthalimido, pyrrolidinyl, pyridyl, various (un)substituted NH2 groups, piperidinyl, quinuclidinyl; R3 = alkyl, haloalkyl, alkoxy, OH, halo, CO2H, Ph, phenylalkoxy, alkenyloxy, alkanoylalkoxy, alkylaminocarbonylalkoxy; n = 0, 1, 2; optional 3,4-double bond], some of which are novel and/or prepd., are useful as antiarrhythmics. For example, cyclization of 2-[2-(4-benzyl-1-piperidinyl)acetyl]amino-3-methylbenzaldehyde by NaOEt in refluxing EtOH gave I [R1 = H, R2 = 8-Me, R3 = 3-(4-benzyl-1-piperidinyl); .DELTA.3 present], isolated as the HCl salt. Various I were active at 3-300 .mu.mol doses when tested against elec.-stimulated contractions of isolated feline **cardiac** muscle samples. Approx. 170 I (free bases and/or salts) are listed with phys. data, and antiarrhythmic test data are given for 27 compds.

IT **113226-24-7**
RL: RCT (Reactant)
(prepn. as antiarrhythmic)

RN 113226-24-7 CAPLUS
CN 2(1H)-Quinolinone, 1,8-dimethyl-4-(1-pyrrolidinyl)-, monohydrochloride (9CI) (CA INDEX NAME)



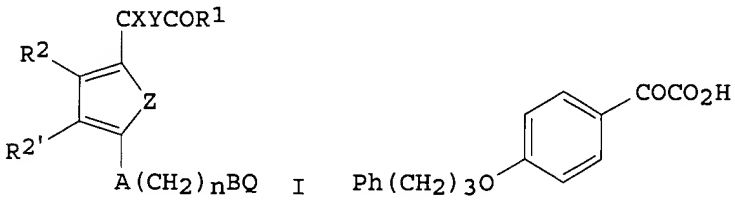
● HCl

L5 ANSWER 37 OF 61 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1993:147306 CAPLUS
DOCUMENT NUMBER: 118:147306
TITLE: Preparation of .alpha.-oxobenzeneacetic acids and related compounds as antiischemics and antiarrhythmics
INVENTOR(S): Guthrie, Robert William; Heathers, Guy Phillip; Higgins, Alan John; Kachensky, David Francis; Kierstead, Richard Wightmann; LeMahieu, Ronald Andrew; Mullin, John Guilfoyle, Jr.; Tilley, Jefferson Wright
PATENT ASSIGNEE(S): Hoffmann-La Roche, F., AG, Switz.
SOURCE: Eur. Pat. Appl., 166 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 512352	A2	19921111	EP 1992-107135	19920427
EP 512352	A3	19930310		
EP 512352	B1	19960327		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, MC, NL, PT, SE				
US 5344843	A	19940906	US 1992-850620	19920313

PRIORITY APPLN. INFO.: US 1991-698014 A 19910509
US 1992-850620 A 19920313
OTHER SOURCE(S): MARPAT 118:147306
GI

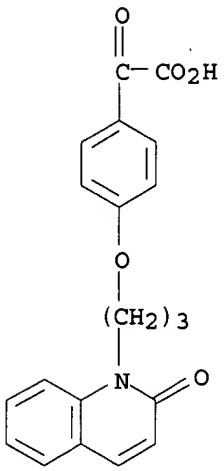


AB Title compds. I [R1 = OH, OR3, NR4R5; 1 of R4, R5 = H, C1-7 (hydroxy)alkyl and the other = H, OH, C1-7 alkyl, C1-7 alkoxy; R3 = (CH2CH2O)mH, CH2CHOHCH2OH, 2,2-dimethyl-1,3-dioxolan-4-yl, CH2CH2NH2, etc.; m = 1-4; R2, R2' = H, C1-7 alkyl, aryl-C1-7 alkyl, C1-7 alkoxy, OH, NH2, C1-7 alkylamino, cyano, halo, SH, etc.; A = bond, O, NR7, S, SO, SO2, C.tplbond.C, CH:CH, CH2CH, NR8CO, CONR9; R7 = H, C1-7 alkyl, acyl; R8,R9 = H, C1-7 alkyl; n = 0-10; B = bond, groups defined for A, CO, CS, (OCH2CH2)mO, etc.; Z = O, S, CR2:CR2', N:CR2, CR2:N, NR11; R11 = H, C1-7 alkyl; XY = O, S, :NOH, alkoxyimino, alkenyloxyimino, hydrazono, etc., or individually 1 of X and Y = halo and the other = H, halo, C1-7 alkyl, aryl-C1-7 alkyl; other possibilities for X and Y; Q = cycloalkyl, aryl, heterocyclyl; with provisos] were prepd. as drugs to prevent injury to ischemic tissue and arrhythmias during and after a myocardial **infarction**. Thus, Me 4-hydroxy-.alpha.-oxobenzeneacetate in DMF contg. NaH was O-alkylated by Ph(CH2)3Br and the resultant product was hydrolyzed by NaOH in MeOH to give title compd. II. II had IC50 of 0.5 .mu.M against carnitine acyltransferase 1 in mitochondria. Over 200 I were prepd. Capsules contg. I were also prepd.

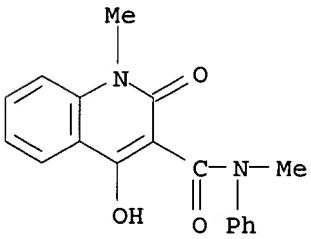
IT **145795-79-5P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as antiischemic and antiarrhythmic)

RN 145795-79-5 CAPLUS

CN Benzeneacetic acid, .alpha.-oxo-4-[3-(2-oxo-1(2H)-quinolinyl)propoxy]- (9CI) (CA INDEX NAME)



L5 ANSWER 38 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1992:543011 CAPLUS
DOCUMENT NUMBER: 117:143011
TITLE: Mode of action of immunosuppressive drugs evaluated with the aid of the immunostimulator LS-2616: studies on rejecting rat **cardiac** allografts
AUTHOR(S): Wanders, A.; Gannedahl, G.; Gerdin, B.; Tufveson, G.
CORPORATE SOURCE: Dep. Urol., Univ. Hosp., Uppsala, S-751 85, Swed.
SOURCE: Transplant. Proc. (1992), 24(1), 274-5
CODEN: TRPPA8; ISSN: 0041-1345
DOCUMENT TYPE: Journal
LANGUAGE: English
AB LS-2616, which induces the rejection of **cardiac** allografts in rats while still on treatment with cyclosporine A or prednisolose, had a considerably weaker effect on grafts protected with deoxyspergualine.
IT **84088-42-6**, LS-2616
RL: BIOL (Biological study)
(heart allograft rejection response to)
RN 84088-42-6 CAPLUS
CN 3-Quinolinecarboxamide, 1,2-dihydro-4-hydroxy-N,1-dimethyl-2-oxo-N-phenyl- (9CI) (CA INDEX NAME)



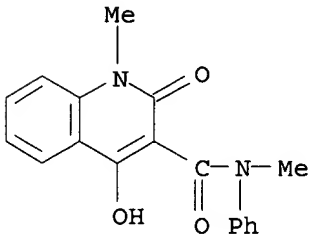
L5 ANSWER 39 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1992:120595 CAPLUS
DOCUMENT NUMBER: 116:120595
TITLE: Mode of action of immunosuppressive drugs evaluated with the aid of the immunostimulator LS-2616: studies on rejecting rat **cardiac** allografts

AUTHOR(S): Wanders, A.; Gannedahl, G.; Gerdin, B.; Tufveson, G.
CORPORATE SOURCE: Dep. Urol., Univ. Hosp., Uppsala, S-751 85, Swed.
SOURCE: Transplant. Proc. (1992), 24(1), 274-5
CODEN: TRPPA8; ISSN: 0041-1345
DOCUMENT TYPE: Journal
LANGUAGE: English

AB There is a certain drug selectivity in the effect of LS-2616 to promote rejection of immunosuppressed rat **cardiac** allografts. LS-2616 thus fully abrogated the immunosuppressive effects of cyclosporine and prednisolone, but not of 15-deoxyspergualin. LS-2616 may serve as a delicate tool in evaluating the mode of action of these different immunosuppressive drugs in order to identify an optimal antirejection regime.

IT **84088-42-6**, LS 2616
RL: BIOL (Biological study)
(heart transplant rejection suppression by immunosuppressants antagonism by, in rat model)

RN 84088-42-6 CAPLUS
CN 3-Quinolinecarboxamide, 1,2-dihydro-4-hydroxy-N,1-dimethyl-2-oxo-N-phenyl- (9CI) (CA INDEX NAME)

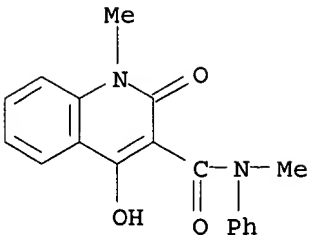


L5 ANSWER 40 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1989:417327 CAPLUS
DOCUMENT NUMBER: 111:17327
TITLE: Rat **cardiac** allografts protected with cyclosporin A are rejected in the presence of LS-2616 (Linomide)
AUTHOR(S): Gerdin, Bengt; Wanders, Alkwin; Tufveson, Gunnar
CORPORATE SOURCE: Dep. Surg., Univ. Uppsala, Uppsala, Swed.
SOURCE: Transplant. Proc. (1989), 21(1, Book 1), 853-5
CODEN: TRPPA8; ISSN: 0041-1345
DOCUMENT TYPE: Journal
LANGUAGE: English

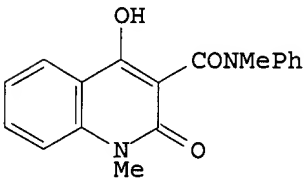
AB Untreated rats rejected heart transplants at .apprx.8 days. Oral treatment with cyclosporin A at 2 mg/kg did not affect the day of rejection whereas 5 mg/kg prolonged the graft survival. LS-2616 at 160 mg/kg/day abrogated the protective effects of cyclosporin A at 10 mg/kg on heart graft survival, but LS-2616 had no effect alone. The immunosuppression by prednisolone also was reversed by LS-2616. Thus, LS-2616 may prove useful in reversing overimmunosuppression.

IT **84088-42-6**, LS 2616
RL: BIOL (Biological study)
(immunosuppression by cyclosporine or prednisolone reversal by, heart transplant survival response to)

RN 84088-42-6 CAPLUS
CN 3-Quinolinecarboxamide, 1,2-dihydro-4-hydroxy-N,1-dimethyl-2-oxo-N-phenyl- (9CI) (CA INDEX NAME)



L5 ANSWER 41 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1989:185373 CAPLUS
DOCUMENT NUMBER: 110:185373
TITLE: Abolition of the effect of cyclosporine on rat **cardiac** allograft rejection by the new immunomodulator LS-2616 (Linomide)
AUTHOR(S): Wanders, Alkwin; Larsson, Erik; Gerdin, Bengt; Tufveson, Gunnar
CORPORATE SOURCE: Dep. Surg., Univ. Uppsala, Uppsala, Swed.
SOURCE: Transplantation (1989), 47(2), 216-17
CODEN: TRPLAU; ISSN: 0041-1337
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

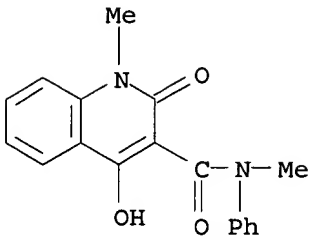


I

AB The effect of the quinoline-3-carboxamide LS-2616 (Linomide)(I) given alone or together with cyclosporine, was studied in the 1st-set **cardiac** allograft transplantation model in the rat. PVG rat hearts were transplanted heterotopically to Wistar/Kyoto rat recipients on day 0. The recipients were given LS-2616 orally on day 1 to rejection and/or CsA orally on days 0-9. In untreated animals rejection occurred on days 8-9. Treatment with CsA (5 or 10 mg/kg) resulted in prolongation of graft survival to days 17-21, i.e., the rejection occurred 8-10 days after cessation of treatment. LS-2616 at 160 mg/kg did not in itself have any impact on graft survival, but, when given at 40 or 160 mg/kg simultaneously with CsA (10 mg/kg), the effect of CsA was totally abolished. Animals treated with LS-2616 together with CsA had slightly lower trough blood levels than those treated with CsA alone. This interaction with CsA pharmacokinetics does not explain the results, as doubling of the CsA dose to 20 mg/kg, which well compensated for the difference in blood levels, was not sufficient to reverse the effect of LS-2616. This compd. abolishes the effect of CsA.

IT **84088-42-6**, LS 2616
RL: BIOL (Biological study)
(heart allograft survival response to cyclosporine inhibition by)

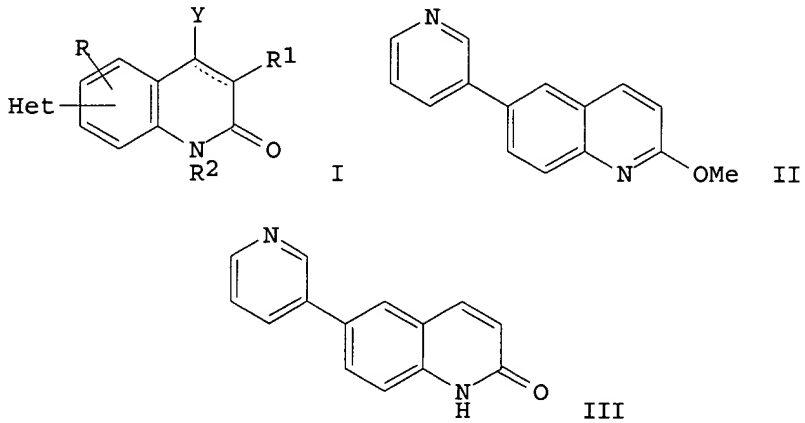
RN 84088-42-6 CAPLUS
CN 3-Quinolinecarboxamide, 1,2-dihydro-4-hydroxy-N,1-dimethyl-2-oxo-N-phenyl- (9CI) (CA INDEX NAME)



L5 ANSWER 42 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1989:114694 CAPLUS
DOCUMENT NUMBER: 110:114694
TITLE: Process for preparing quinolone derivatives
INVENTOR(S): Roberts, David Anthony; Campbell, Simon Fraser
PATENT ASSIGNEE(S): Pfizer Corp., USA
SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, 136 pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 85100796	A	19861001	CN 1985-100796	19850401

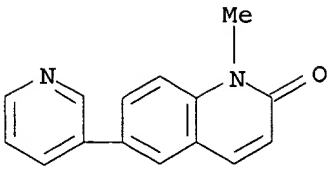
GI



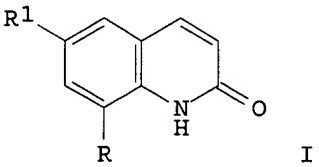
AB The title compds. [I; Het = heteroaryl; R = H, alkyl, alkoxy, etc.; R1 = H, cyano, halo, amino, etc.; R2 = H, alkyl, HOCH2CH2; Y = H, alkyl; the dotted line indicates single or double bond], useful as **cardiac** stimulants (no data), are prepd. by various routes. E.g., a soln. of 1.83 g methoxyquinoline deriv. II in aq. HBr was heated at 100.degree. for 1.5 h to give 0.62 g quinolinone III. About 100 I were prepd.

IT **99471-47-3P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as **cardiac** stimulant)

RN 99471-47-3 CAPLUS
CN 2(1H)-Quinolinone, 1-methyl-6-(3-pyridinyl)- (9CI) (CA INDEX NAME)



L5 ANSWER 43 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1988:528805 CAPLUS
DOCUMENT NUMBER: 109:128805
TITLE: 2(1H)-Quinolinones with **cardiac** stimulant activity. 1. Synthesis and biological activities of (six-membered heteroaryl)-substituted derivatives
AUTHOR(S): Alabaster, Colin T.; Bell, Andrew S.; Campbell, Simon F.; Ellis, Peter; Henderson, Christopher G.; Roberts, David A.; Ruddock, Keith S.; Samuels, Gillian M. R.; Stefaniak, Mark H.
CORPORATE SOURCE: Dep. Discovery Biol., Pfizer Cent. Res., Sandwich/Kent, UK
SOURCE: J. Med. Chem. (1988), 31(10), 2048-56
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 109:128805
GI

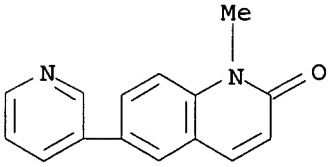


I

AB A series of (six-membered heteroaryl)-substituted 2(1H)-quinolinones, e.g., I (R = H, R1 = pyridin-2-yl), were synthesized, and structure-activity relationships for **cardiac** stimulant activity were detd. Most compds. were prepd. by acidic hydrolysis of a heteroaryl-2-methoxyquinoline obtained by palladium-catalyzed cross-coupling methodol. Direct reaction of a pyridinylzinc reagent with a 6-haloquinolinone also proved successful. In anesthetized dogs, I (R = H, R1 = pyridin-3-yl)(II) (50 .mu.g/kg) displayed greater inotropic activity (percentage increase in dP/dt max) than positional isomers, and potency was maintained with either mono- or di- alkylpyridinyl substituents. Introduction of a 4- or 7-Me group into II reduced inotropic activity, whereas the 8-isomer I (R = Me, R1 = pyridin-3-yl)(III) proved to be the most potent member of the series. III and the 2,6-dimethylpyridinyl analog I (R = Me, R1 = 2,6-dimethylpyridin-3-yl)(IV) were approx. 6 and 3 times, resp., more potent than milrinone. Several quinolinones displayed pos. inotropic activity (decrease in QA interval) in conscious dogs after oral administration (1 mg/kg), and III and IV were again the most potent members of the series. IV (0.25, 0.5, 1.0 mg/kg po) demonstrated dose-related **cardiac** stimulant activity, which was maintained for at least 4 h. No changes in heart rate were obsd. Compds. II, III, IV, and I (R = H, R1 = pyridin-4-yl) also selectively stimulated the force of contraction, rather than heart rate, in the dog heart-lung prepn. For a 50% increase in dP/dt max with IV, heart rate changed by less than 10 beats/min. In norepinephrine contracted rabbit femoral artery and saphenous vein, IV produced dose

related (5 .times. 10-7 to 5 .times. 10-4 M) vasorelaxant activity. The combined **cardiac** stimulant and vasodilator properties displayed by IV, coupled with a lack of effect on heart rate, should be beneficial for the treatment of congestive heart failure.

IT **99471-47-3P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)
RN 99471-47-3 CAPLUS
CN 2(1H)-Quinolinone, 1-methyl-6-(3-pyridinyl)- (9CI) (CA INDEX NAME)

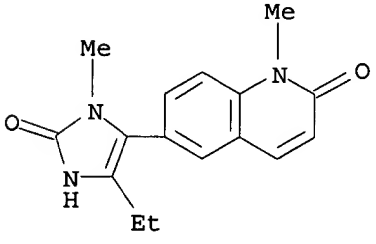


L5 ANSWER 44 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1987:18559 CAPLUS
DOCUMENT NUMBER: 106:18559
TITLE: 4-Imidazolin-2-one derivatives
INVENTOR(S): Takatani, Takao; Takasugi, Hisashi; Nishino, Shigetaka
PATENT ASSIGNEE(S): Fujisawa Pharmaceutical Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 23 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 61191681	A2	19860826	JP 1985-33342	19850221

GI For diagram(s), see printed CA Issue.
AB The title compds. [I; R1 = H, alkyl, cyclo-, alkenyl-, alkynyl-, halo-, piperazinyl-, or (alkylamino)alkyl; R2 = H, alkyl, carboxy- or alkoxycarbonylalkyl; X = part of a heterocyclic ring], useful as **cardiac** stimulants (no data), were prepd. Thus, benzoxazoline II [R3 = H2NCHMeCO].HCl was heated with MeNCO in pyridine at 50.degree. for 2 h to give II [R3 = 3,5-dimethyl-2-oxo-4-imidazolin-4-yl].

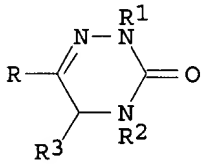
IT **105743-01-9P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as **cardiac** stimulant)
RN 105743-01-9 CAPLUS
CN 2(1H)-Quinolinone, 6-(5-ethyl-2,3-dihydro-3-methyl-2-oxo-1H-imidazol-4-yl)-1-methyl- (9CI) (CA INDEX NAME)



L5 ANSWER 45 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1985:149290 CAPLUS
DOCUMENT NUMBER: 102:149290
TITLE: Triazine derivatives and pharmaceutical compositions comprising them
INVENTOR(S): Teraji, Tsutomu; Shiokawa, Youichi; Okumura, Kazuo; Sato, Yoshinari
PATENT ASSIGNEE(S): Fujisawa Pharmaceutical Co., Ltd. , Japan
SOURCE: Eur. Pat. Appl., 80 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 122494	A2	19841024	EP 1984-103030	19840320
EP 122494	A3	19861126		
R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
US 4581356	A	19860408	US 1984-588343	19840312
DK 8401628	A	19840923	DK 1984-1628	19840321
JP 59181275	A2	19841015	JP 1984-55552	19840322
PRIORITY APPLN. INFO.:			GB 1983-7831	19830322
			GB 1983-10437	19830418

GI

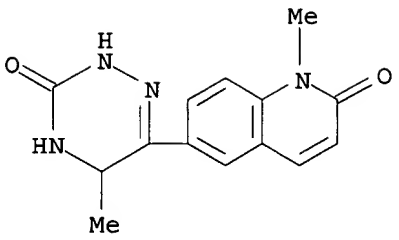


I

AB The triazine derivs. I [R = (un)substituted 1,2,3,4-tetrahydroquinolyl, 2-oxo-1,2,3,4-tetrahydroquinolyl, 2-oxo-1,2-dihydroquinolyl, indolyl, 2-oxindolinyl, benzothiazolyl, 2-oxobenzothiazolinyl, 3,4-dihydro-1H-2,1-benzothiazinyl in which the S atom may be oxidized, or 3-oxo-2,3-dihydro-4H-1,4-benzoxazinyl; R1 = H, alkenyl, PhCH2, carboxyalkyl, alkoxycarbonylalkyl; R2, R3 = H, alkyl; R2R3 = bond] were prepd. for treatment of hypertension, **thrombosis**, and ulcer. Thus, 1-methyl-2-oxo-1,2,3,4-tetrahydroquinoline was treated with 2-phthalimidoacetyl chloride and AlCl3 followed by hydrolysis to give 6-(aminoacetyl)-1-methyl-2-oxo-1,2,3,4-tetrahydroquinoline-HCl, which was treated with EtO2CCOCl and the product cyclized with H2NNH2.H2O to give 6-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-4,5-dihydro-1,2,4-triazin-3(2H)-one (II). At 1 mg/kg II reduced the blood pressure in rats by 49%. The platelet aggregation inhibition ID50 of II was 3.6 .times. 10-7, and at 32 mg/kg II inhibited ulcers in rats by 80%.

IT **95657-68-4P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and antihypertensive and platelet aggregation inhibition activity of)

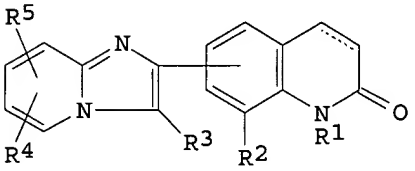
RN 95657-68-4 CAPLUS
CN 2(1H)-Quinolinone, 1-methyl-6-(2,3,4,5-tetrahydro-5-methyl-3-oxo-1,2,4-triazin-6-yl)- (9CI) (CA INDEX NAME)



L5 ANSWER 46 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1983:493757 CAPLUS
DOCUMENT NUMBER: 99:93757
TITLE: Carbostyrils as heart stimulants
PATENT ASSIGNEE(S): Otsuka Pharmaceutical Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 30 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 58096022	A2	19830607	JP 1981-193431	19811130
JP 01033083	B4	19890711		

GI

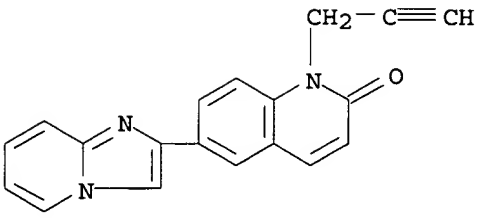


I

AB Carbostyrils I (R1 = H, alkyl, alkenyl, etc.; R2 = H, alkyl, alkoxy, OH, or halogen; R3 = H, alkyl, nitroso, etc.; R4 and R5 = H, halogen, NO2, etc.) are **cardiac** stimulants, and their synthesis and formulations described. Thus, 6-(3-methylimidazo[1,2-a]pyridin-2-yl)-1-methyl-3,4-dihydrocarbostyril-HBr (II) [83229-25-8] was prepd. by treating 6-(.alpha.-bromopropionyl)-1-methyl-3,4-dihydrocarbostyril [83229-24-7] with 2-aminopyridine [504-29-0]. Tablets were prepd. contg. 10 mg II. **Cardiac** stimulation by II in dogs is demonstrated.

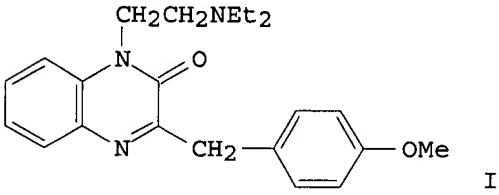
IT **83229-71-4P**
RL: PREP (Preparation)
(prepn. of, as heart stimulant)

RN 83229-71-4 CAPLUS
CN 2(1H)-Quinolinone, 6-imidazo[1,2-a]pyridin-2-yl-1-(2-propynyl)-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

L5 ANSWER 47 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1982:97429 CAPLUS
DOCUMENT NUMBER: 96:97429
TITLE: Electromechanical effects of caroverine, a new slow-channel blockade, on the SA node cells of rabbit and atrial muscle fibers of rabbit and guinea pig
AUTHOR(S): Ikeda, Nobuo; Kodama, Itsuo; Shibata, Shoji; Kondo, Noriaki; Yamada, Kazuo
CORPORATE SOURCE: Res. Inst. Environ. Med., Nagoya Univ., Nagoya, Japan
SOURCE: J. Cardiovasc. Pharmacol. (1982), 4(1), 70-5
CODEN: JCPCDT; ISSN: 0160-2446
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

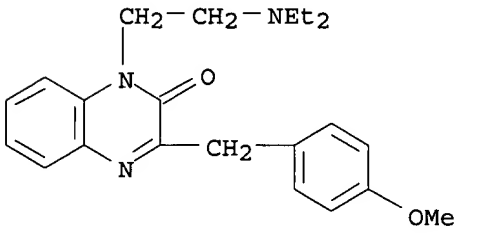


I

AB The effects of caroverine (I) [**23465-76-1**] on elec. activity of isolated rabbit sinoatrial (SA) node cells and atrial muscle fibers and on contractile force of atrial muscle prepns. were examd. In spontaneously firing SA node cells, caroverine (1 .times. 10-7-1 .times. 10-5 M) decreased the action potential amplitude and the max. rate of depolarization in a concn.-dependent manner. However, the spontaneous firing cycle length of these cells was not prolonged significantly with the drug except at a high concn. In constantly driven atrial muscle fibers, caroverine at the same concn. range shortened the 30% repolarization time coupled with a depression of the plateau phase of action potentials. The effects of caroverine on the developed tension (DT) of atrial muscle were compared with those of verapamil. The 50% ED50 for inhibition on atrial DT was 1 .times. 10-5 M for caroverine and 8 .times. 10-8 M for verapamil. Caroverine as well as verapamil had a frequency-dependent inhibitory action on atrial DT, which indicates that both of the drugs have an influence on the kinetics of the slow channel of **cardiac** fibers. Apparently, caroverine has only a small neg. inotropic effect while electrophysiol. effects are similar to slow-channel blockers.

IT **23465-76-1**
RL: BIOL (Biological study)

(heart contraction and elec. activity response to)
RN 23465-76-1 CAPLUS
CN 2(1H)-Quinoxalinone, 1-[2-(diethylamino)ethyl]-3-[(4-methoxyphenyl)methyl]-(9CI) (CA INDEX NAME)

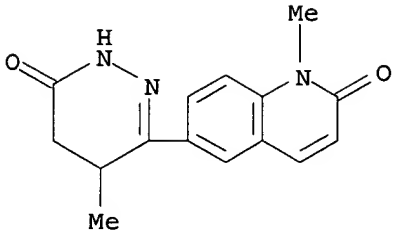


L5 ANSWER 48 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1981:65712 CAPLUS
DOCUMENT NUMBER: 94:65712
TITLE: Antithrombotic and antihypertensive pyridazinone derivatives
INVENTOR(S): Nakao, Toru; Setoguchi, Shinro; Yaoka, Osamu
PATENT ASSIGNEE(S): Yoshitomi Pharmaceutical Industries, Ltd., Fr.
SOURCE: Fr. Demande, 25 pp.
CODEN: FRXXBL
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 2439196	A1	19800516	FR 1978-29496	19781017
US 4258185	A	19810324	US 1980-139625	19800414

PRIORITY APPLN. INFO.: FR 1978-29496 19781017
US 1978-952183 19781017

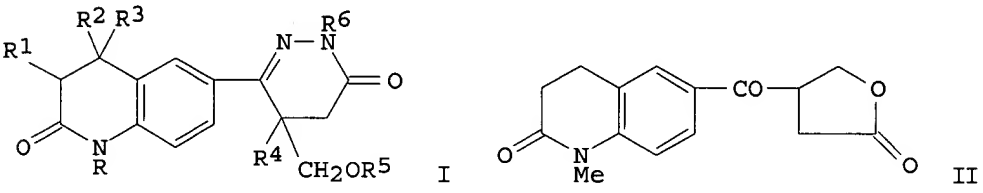
GI For diagram(s), see printed CA Issue.
AB Title pyridazinones I [X = (un)substituted CH2, CH2CH2; X1 = O, CH2; R = H, alkyl, alkanoyl, alkanesulfonyl, Bz; R1 = H, alkyl, hydroxyalkyl, carbamoylalkyl, naphthyloxyalkyl, oxoalkyl, R5R6N(CH2)n (R5, R6 = H, alkyl; R5R6N = heterocycle, i.e. morpholino; n = 2,3); R2 = H, R3 = H, alkyl, HOCH2, alkanoyloxymethyl; R4 = H, alkyl] and their salts were prepd. Thus, the cyclocondensation of indoline II and N2H4 gave I (X = CH2, X1 = O, R = Me, R1-R4 = H). I (X = CH2CH2, X1 = O, R = Me, R1 = R3 = R4 = H, R2 = Me) at 0.03 mg/kg in rats gave 62% inhibition of blood platelet aggregation and was antihypertensive in rats.
IT **71008-88-3P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)
RN 71008-88-3 CAPLUS
CN 2(1H)-Quinolinone, 1-methyl-6-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)- (9CI) (CA INDEX NAME)



L5 ANSWER 49 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1980:620765 CAPLUS
DOCUMENT NUMBER: 93:220765
TITLE: Pyridazinone derivatives
PATENT ASSIGNEE(S): Yoshitomi Pharmaceutical Industries, Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 4 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 55053284	A2	19800418	JP 1978-125801	19781012
JP 62057627	B4	19871202		

GI

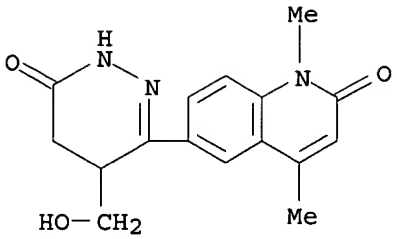


AB Pyridazinone derivs. (I; R, R2, R3, R4, R6 = H, alkyl; R1 = H, R1R2 = bond; R5 = H, acyl), effective blood platelet aggregation inhibitors, antihypertensives, and antithrombics at 1-1000 mg in adults, were prepd. Thus, a mixt. of 4.9 g II and 3.0 mL 85% N2H4.H2O in EtOH was refluxed overnight to give 2.5 g I (R = Me, R1-R6 = H). Similarly prepd. were 12 addnl. I.

IT **75545-19-6P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)

RN 75545-19-6 CAPLUS

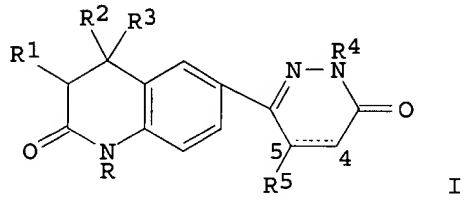
CN 2(1H)-Quinolinone, 1,4-dimethyl-6-[1,4,5,6-tetrahydro-4-(hydroxymethyl)-6-oxo-3-pyridazinyl]- (9CI) (CA INDEX NAME)



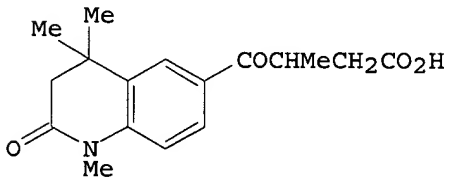
L5 ANSWER 50 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1980:620764 CAPLUS
DOCUMENT NUMBER: 93:220764
TITLE: Pyridazine derivatives
PATENT ASSIGNEE(S): Yoshitomi Pharmaceutical Industries, Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 6 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 55053283	A2	19800418	JP 1978-125800	19781012
JP 61052833	B4	19861114		

GI



I



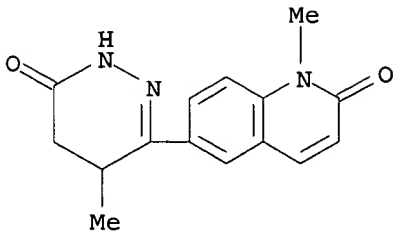
II

AB Pyridazinone derivs. (I; R, R2, R3, R4, R5 = H, alkyl; R1 = H, R1R2 = bond; C-4-5 satd. or unsatd.), effective blood platelet aggregation inhibitors, antihypertensives, and antithrombics at 1-1000 mg in adults, were prepd. Thus, a mixt. of 20 g II and 10 g N2H4.H2O in EtOH was refluxed 1 h to give 15.1 g I (R = R2 = R3 = R5 = Me, R1 = R4 = H, C-4-5 satd.). Similarly prepd. were 17 addnl. I.

IT **71008-88-3P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)

RN 71008-88-3 CAPLUS

CN 2(1H)-Quinolinone, 1-methyl-6-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)- (9CI) (CA INDEX NAME)

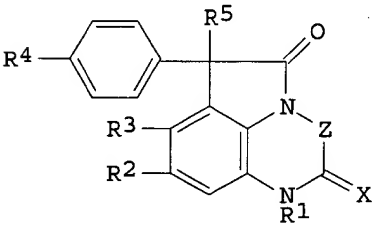


L5 ANSWER 51 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1978:509587 CAPLUS
DOCUMENT NUMBER: 89:109587
TITLE: Substituted pyrroloquinoxalinones and diones
INVENTOR(S): Holmes, Richard E.
PATENT ASSIGNEE(S): Lilly, Eli, and Co., USA
SOURCE: U.S., 7 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

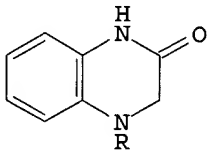
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 4087527	A	19780502	US 1977-836830	19770926
US 4075206	A	19780221	US 1977-772154	19770225
US 30415	E	19801007	US 1979-42848	19790529

PRIORITY APPLN. INFO.: US 1977-772154 19770225
US 1977-836830 19770926

GI



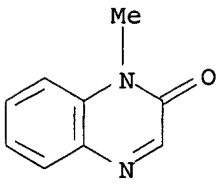
I



II

AB The title compds. I [R1 = H, C1-3 alkyl; R2 = H, C1-3 alkyl, C1-3 alkoxy, Cl; R3 = H; R2R3 = (CH2)4; R4 = H, Cl, F; R5 = OH, H, Ph; X = O, H2; Z = (CH2)2, CHR6 (R6 = H, C1-3 alkyl)], useful as **thrombosis** inhibitors, were prepd. by acylation of a quinoxaline, benzodiazepine, or benzoquinoxaline deriv. with an arylacetyl halide to give an amide which was cyclized with polyphosphoric acid. Thus, the quinoxalinone II (R = H) was acylated with PhCHClCOCl to give II (R = PhCHClCO), which was cyclized with polyphosphoric acid to give I (R1-R5 = H, X = O, Z = CH2).

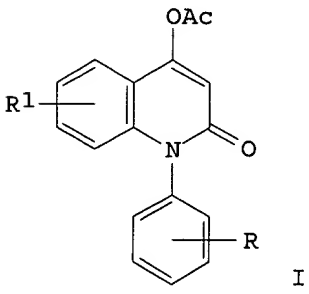
IT **6479-18-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and hydrogenation of)
RN 6479-18-1 CAPLUS
CN 2(1H)-Quinoxalinone, 1-methyl- (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



L5 ANSWER 52 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1978:509139 CAPLUS
DOCUMENT NUMBER: 89:109139
TITLE: Quinolone derivatives
INVENTOR(S): Schacht, Erich; Dahm, Hans; Lissner, Reinhard
PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Ger.
SOURCE: Ger. Offen., 13 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 2651581	A1	19780518	DE 1976-2651581	19761112
US 4168312	A	19790918	US 1977-849585	19771108
BE 860707	A1	19780510	BE 1977-182529	19771110
SE 7712725	A	19780513	SE 1977-12725	19771110
FR 2375215	A1	19780721	FR 1977-34039	19771110
AU 7730546	A1	19790517	AU 1977-30546	19771110
AU 510306	B2	19800619		
AT 7708039	A	19800915	AT 1977-8039	19771110
AT 361928	B	19810410		
CA 1099721	A1	19810421	CA 1977-290590	19771110
NL 7712447	A	19780517	NL 1977-12447	19771111
JP 53063387	A2	19780606	JP 1977-136152	19771111
ZA 7706752	A	19780927	ZA 1977-6752	19771111
ES 464068	A1	19790101	ES 1977-464068	19771111
GB 1547729	A	19790627	GB 1977-47125	19771111
HU 175130	P	19800528	HU 1977-ME2121	19771111

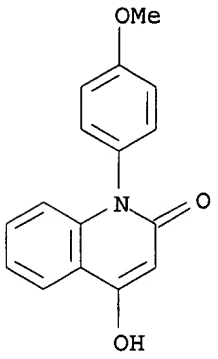
PRIORITY APPLN. INFO.: DE 1976-2651581 19761112
GI



I

AB The quinolones I (R = R1 = H, F, Cl, Br, CF3, MeO) were prepd. for use as antithrombotics at 10-5000 mg. Thus, 2-(4-MeOC6H4NH)C6H4CO2H was heated with AcOH and Ac2O to give I (R = 4-MeO, R1 = H).
IT **67160-11-6P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and chlorination of)
RN 67160-11-6 CAPLUS
CN 2(1H)-Quinolinone, 4-hydroxy-1-(4-methoxyphenyl)- (9CI) (CA INDEX NAME)



L5 ANSWER 53 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1977:535113 CAPLUS
DOCUMENT NUMBER: 87:135113
TITLE: Antithrombogenic carbostyril carboxyalkoxy derivatives
PATENT ASSIGNEE(S): Otsuka Pharmaceutical Co., Ltd., Japan
SOURCE: Ger. Offen., 116 pp. Division of Ger. Offen. 2,527,937.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

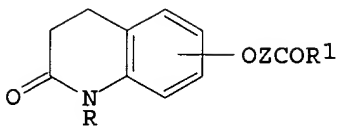
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 2559509	A1	19761230	DE 1975-2559509	19750623
DE 2559509	C2	19830217		
JP 51001480	A2	19760108	JP 1974-72472	19740624
JP 52039831	B4	19771007		
JP 51001481	A2	19760108	JP 1974-72473	19740624
JP 52039832	B4	19771007		
JP 51006970	A2	19760120	JP 1974-77660	19740705
JP 51082279	A2	19760719	JP 1974-77661	19740705
JP 51023271	A2	19760224	JP 1974-94376	19740816
JP 51128976	A2	19761110	JP 1975-53026	19750430
JP 51128977	A2	19761110	JP 1975-53027	19750430
JP 51128978	A2	19761110	JP 1975-53028	19750430
JP 51133276	A2	19761118	JP 1975-58127	19750515
JP 51133277	A2	19761118	JP 1975-58128	19750515
JP 51133278	A2	19761118	JP 1975-58129	19750515
JP 51133283	A2	19761118	JP 1975-58134	19750515
JP 57040146	B4	19820825		
JP 51133284	A2	19761118	JP 1975-58135	19750515
JP 51136676	A2	19761126	JP 1975-58872	19750516
JP 60004173	B4	19850201		
JP 51136677	A2	19761126	JP 1975-58874	19750516
JP 53037353	B4	19781007		
JP 51141864	A2	19761207	JP 1975-66729	19750602
JP 57000855	B4	19820108		
BE 830524	A1	19751016	BE 1975-157579	19750623
NL 7507462	A	19751230	NL 1975-7462	19750623

NL 162376	B	19791217			
NL 162376	C	19800516			
ZA 7504000	A	19760929	ZA 1975-4000	19750623	
SU 667133	D	19790605	SU 1975-2151951	19750623	
SE 7507216	A	19751229	SE 1975-7216	19750624	
SE 434639	B	19840806			
SE 434639	C	19841115			
ES 438836	A1	19770601	ES 1975-438836	19750624	
AT 351029	B	19790710	AT 1978-1052	19780214	
AT 7801052	A	19781215			
DK 7900680	A	19790216	DK 1979-680	19790216	
DK 150300	B	19870202			
DK 150300	C	19871123			
US 4313947	A	19820202	US 1979-58467	19790718	
CH 625508	A	19810930	CH 1980-8481	19801114	
CH 626878	A	19811215	CH 1980-8482	19801114	

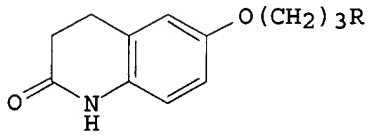
PRIORITY APPLN. INFO.:

JP 1974-72472	19740624
JP 1974-72473	19740624
JP 1974-77660	19740705
JP 1974-77661	19740705
JP 1974-94376	19740816
JP 1975-53026	19750430
JP 1975-53027	19750430
JP 1975-53028	19750430
JP 1975-58127	19750515
JP 1975-58128	19750515
JP 1975-58129	19750515
JP 1975-58134	19750515
JP 1975-58135	19750515
JP 1975-58872	19750516
JP 1975-58874	19750516
JP 1975-66729	19750602
US 1975-588475	19750619
CH 1975-8151	19750623
DK 1975-2831	19750623
US 1977-806926	19770615
AT 1975-4843	19780214

GI



I



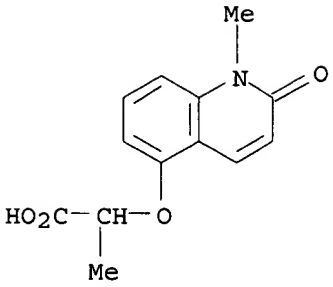
II

AB Carbostyril derivs. I [R = H, Me, allyl, PhCH2, etc.; R1 = OH, OMe, OCH2Ph, NH2, NMe2, etc.; Z = (CH2)n (n = 1-10), branched alkylene] were prepd. for use as antithrombics. Thus, II (R = CN) was refluxed with aq. KOH, followed by acidification with HCl to give II (R = CO2H). II (R = CO2Et) at 10-4 M gave 100% inhibition of collagen-induced rabbit blood platelet aggregation.

IT **58898-74-1P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)

RN 58898-74-1 CAPLUS

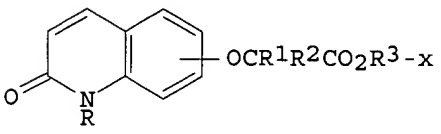
CN Propanoic acid, 2-[(1,2-dihydro-1-methyl-2-oxo-5-quinolinyl)oxy]- (9CI) (CA INDEX NAME)



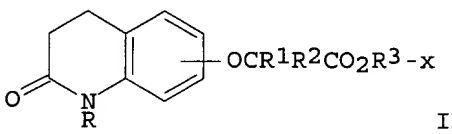
L5 ANSWER 54 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1977:423076 CAPLUS
DOCUMENT NUMBER: 87:23076
TITLE: Carbostyrils
INVENTOR(S): Nakagawa, Kazuyuki; Uchida, Minoru; Oka, Kimiaki
PATENT ASSIGNEE(S): Otsuka Pharmaceutical Co., Ltd., Japan
SOURCE: Japan. Kokai, 11 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 51128981	A2	19761110	JP 1975-53031	19750430
JP 59006859	B4	19840215		

GI



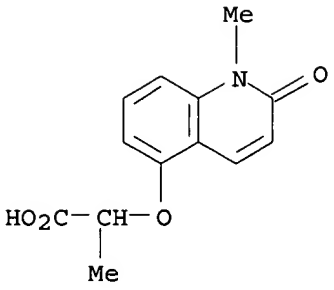
I



II

AB Carbostyrils I (R = H, C1-4 alk(en)yl, aralkyl; R1, R2 = H, C1-4 alkyl; R3 = H, C1-8 alkyl, cycloalkyl, aralkyl) were prepd. by dehydrogenation of their 3,4-dihydro derivs. II. I have antiinflammatory and platelet aggregation inhibitory activities (no data). Thus, 2.6g II (x = 6, R = R2 = H, R1 = Me, R3 = Et) was refluxed with 3.8 g 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in dioxane for 10 h to give 1.9 g corresponding I. Among 29 more I prepd. were (R2 = H) (x, R, R1, and R3 given): 5, H, Me, benzyl; 8 H, H, Et; 5, Me, Me, Et. Chloranil, Raney Ni, or N-bromosuccinimide was also the dehydrogenation agent.

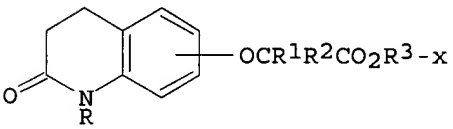
IT **58898-74-1P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)
RN 58898-74-1 CAPLUS
CN Propanoic acid, 2-[(1,2-dihydro-1-methyl-2-oxo-5-quinolinyl)oxy]- (9CI) (CA INDEX NAME)



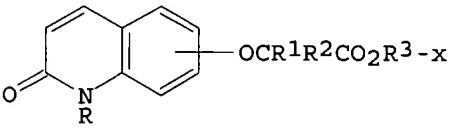
L5 ANSWER 55 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1977:405824 CAPLUS
DOCUMENT NUMBER: 87:5824
TITLE: 3,4-Dihydrocarbostyrils
INVENTOR(S): Nakagawa, Kazuyuki; Uchida, Minoru; Oka, Kimiaki
PATENT ASSIGNEE(S): Otsuka Pharmaceutical Co., Ltd., Japan
SOURCE: Japan. Kokai, 10 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 51128980	A2	19761110	JP 1975-53030	19750430
JP 59006858	B4	19840215		

GI



I

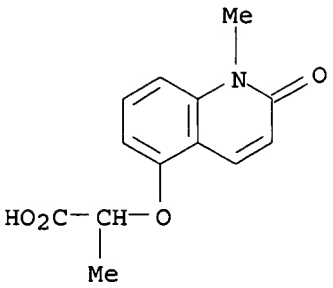


II

AB 3,4-Dihydrocarbostyrils I (R = H, C1-4 alkyl, aralkyl; R1, R2 = H, C1-4 alkyl; R3 = H, C1-8 alkyl, cycloalkyl, aralkyl) were prepd. by hydrogenating carbostyrils II. I have antiinflammatory and platelet aggregation inhibitory activities (no data). Thus, 2.3 g II (x = 5, R = R1 = Me, R2 = R3 = H) was hydrogenated with Pd black in MeOH at 50.degree./2.5 atm for 8 h to give 1.8 g corresponding I. Among 55 more I prepd. were (R = R2 = H) (x, R1, and R3 given): 5, Me, cyclohexyl; 6, Me, n-amyl; 7, Et, Et.

IT **58898-74-1**
RL: RCT (Reactant)
(hydrogenation of)

RN 58898-74-1 CAPLUS
CN Propanoic acid, 2-[(1,2-dihydro-1-methyl-2-oxo-5-quinolinyl)oxy]- (9CI) (CA INDEX NAME)



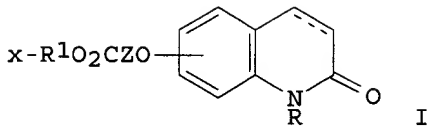
L5 ANSWER 56 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1977:405823 CAPLUS
DOCUMENT NUMBER: 87:5823
TITLE: Carbostyrils
INVENTOR(S): Nakagawa, Kazuyuki; Uchida, Minoru; Oka, Kimiaki
PATENT ASSIGNEE(S): Otsuka Pharmaceutical Co., Ltd., Japan
SOURCE: Japan. Kokai, 7 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 51133277	A2	19761118	JP 1975-58128	19750515
FI 7501842	A	19751225	FI 1975-1842	19750619
FI 59246	B	19810331		
FI 59246	C	19810710		
DK 7502831	A	19751225	DK 1975-2831	19750623
DK 150155	B	19861222		
DK 150155	C	19871109		
NO 7502220	A	19751230	NO 1975-2220	19750623
NO 149106	B	19831107		
NO 149106	C	19840222		
DE 2527937	A1	19760108	DE 1975-2527937	19750623
DE 2527937	C2	19830908		
DE 2559509	A1	19761230	DE 1975-2559509	19750623
DE 2559509	C2	19830217		
AU 7582378	A1	19770106	AU 1975-82378	19750623
CA 1048497	A1	19790213	CA 1975-229940	19750623
CH 621339	A	19810130	CH 1975-8151	19750623
FR 2276043	A1	19760123	FR 1975-19670	19750624
FR 2276043	B1	19780324		
AT 351027	B	19790710	AT 1975-4843	19750624
AT 7504843	A	19781215		
US 4216220	A	19800805	US 1977-806926	19770615
CA 1064036	A2	19791009	CA 1978-315114	19781031
US 4313947	A	19820202	US 1979-58467	19790718

PRIORITY APPLN. INFO.:
JP 1974-72472 19740624
JP 1974-72473 19740624
JP 1974-77660 19740705
JP 1974-77661 19740705
JP 1974-94376 19740816
JP 1975-53026 19750430
JP 1975-53027 19750430
JP 1975-53028 19750430
JP 1975-58127 19750515
JP 1975-58128 19750515
JP 1975-58129 19750515

JP 1975-58134	19750515
JP 1975-58135	19750515
JP 1975-58872	19750516
JP 1975-58874	19750516
JP 1975-66729	19750602
US 1975-588475	19750619
US 1977-806926	19770615

GI



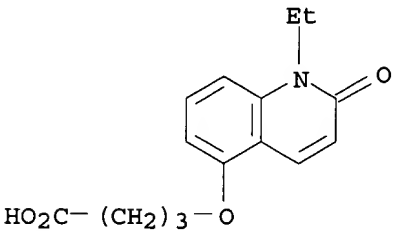
I

AB Forty-six esters I (R = H, Me, Et, allyl, benzyl; R1 = Et, Pr, Me2CH, Bu, n-amyl, isoamyl, benzyl, cyclohexyl; Z = C2-10 alkylene), useful as antiinflammatory and antithrombotic agents (no data), were prepd. by esterification of acids I (R1 = H) (II) with R1OH. Thus, 4.0 g II [3,4-satd., x = 5, Z = (CH2)4, R = H] was refluxed in PrOH in the presence of p-toluenesulfonic acid to give 4.0 g Pr ester.

IT **58899-32-4**
RL: RCT (Reactant)
(esterification of)

RN 58899-32-4 CAPLUS

CN Butanoic acid, 4-[(1-ethyl-1,2-dihydro-2-oxo-5-quinolinyl)oxy]- (9CI) (CA INDEX NAME)



L5 ANSWER 57 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1974:491579 CAPLUS
DOCUMENT NUMBER: 81:91579
TITLE: Quinoxalines
INVENTOR(S): Inoue, Michiro; Ishikawa, Masayuki; Tsuchiya, Takashi; Shimamoto, Takio
SOURCE: Japan. Kokai, 7 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 49024984	A2	19740305	JP 1972-63689	19720627

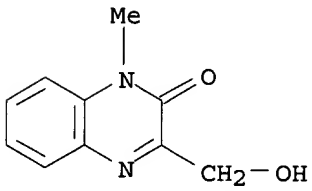
GI For diagram(s), see printed CA Issue.

AB The title compds. I (R1 = H or alkyl; R2 = H, alkyl, cycloalkyl, dialkylaminoalkyl, alkenyl, aryl, or aralkyl; R3 = H or alkyl; R4 and R5 = H, halogen, alkyl, alkoxy, CO2H, or alkoxycarbonyl; R1 and R2 may be an

alkylene optionally interrupted by a hetero atom) were prepd. by treating 2-hydroxy-methyl-3-oxo-3,4-dihydroquinoxalines (II) with R1R2NCOR6 (R6 = halogen, alkoxy, aryloxy, alkylthio, or arylthio) optionally in the presence of a catalyst or dehydrohalogenating agent. I are remedies for arteriosclerosis and **thrombosis**. Thus, 2 g MeNH-COCl was added to a mixt. of 4 g II (R3 = Me, R4 = R5 = H), 3 g PhNMe2, and 40 ml Et2O and the mixt. refluxed 5 hr to give 3.2 g I (R1 = R4 = R5 = H, R2 = R3 = Me). Among ca. 17 more I similarly prepd. were the following (R1-R5 given): H, Me2N(CH2)2, H, H, H; NR1R2 = 4-methylpiperazino, H, H, H; H, Me, H, 6(or 7)-MeO, H; Me, Me, H, 6-Me, 7-Me.

IT **53378-13-5**
RL: RCT (Reactant)
(carbamoylation of)

RN 53378-13-5 CAPLUS
CN 2(1H)-Quinoxalinone, 3-(hydroxymethyl)-1-methyl- (9CI) (CA INDEX NAME)



L5 ANSWER 58 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1974:491578 CAPLUS
DOCUMENT NUMBER: 81:91578
TITLE: Quinoxalines
INVENTOR(S): Inoue, Michiro; Ishikawa, Masayuki; Tsuchiya, Takashi; Shimamoto, Takio
SOURCE: Japan. Kokai, 6 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

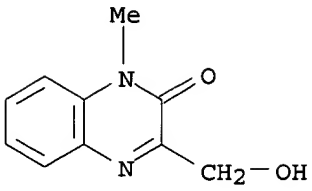
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 49024981	A2	19740305	JP 1972-63686	19720627

GI For diagram(s), see printed CA Issue.

AB The quinoxalines I (R1 = alkyl, cycloakyl, dialkyl-aminoalkyl, alkenyl, aryl, or aralkyl; R2 = H or alkyl; R3 and R4 = H, halo, alkyl, alkoxy, CO2H, or alkoxycarbonyl) were prepd. by treating II with R1NCO. I are remedies for arterio-sclerosis and **thrombosis**. Thus, 2 g II (R2 = Me, R3 and R4 = H) in pyridine was treated overnight with 1 g MeNCO and the mixt. heated 1 hr at 50-60.degree. to give 2 g I (R1 = R2 = Me; R3 = R4 = H). Among 12 more I similarly prepd. were the following (R1-R4 given): Me, H, 6-Me, 7-Me; Me2N(CH2)2, H, H, H; allyl, H, 6-Me, 7-Me; Et2N(CH2)2, H, H, H.

IT **53378-13-5**
RL: RCT (Reactant)
(carbamoylation of, with isocyanates)

RN 53378-13-5 CAPLUS
CN 2(1H)-Quinoxalinone, 3-(hydroxymethyl)-1-methyl- (9CI) (CA INDEX NAME)



L5 ANSWER 59 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1974:491576 CAPLUS
DOCUMENT NUMBER: 81:91576
TITLE: Quinoxalines
INVENTOR(S): Inoue, Michiro; Ishikawa, Masayuki; Tsuchiya, Takashi; Shimamoto, Takio
SOURCE: Japan. Kokai, 7 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

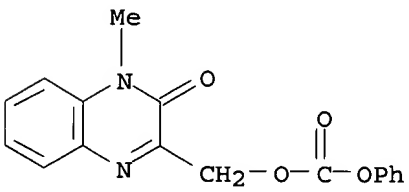
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 49024982	A2	19740305	JP 1972-63687	19720627

GI For diagram(s), see printed CA Issue.

AB The quinoxalines I (R1 = H or alkyl; R2 = H, alkyl, cycloalkyl, dialkylaminoalkyl, alkenyl, aryl, or aralkyl; R3 = H or alkyl; R4,R5 = H, halogen, alkyl, or alkoxy; R1R2 may be alkylene optionally interrupted by a hetero atom) were prepd. by treating II (Z = O or S; R = lower alkyl, aryl, or substituted aryl) with NHR1R2. I are remedies for arterio-sclerosis and **thrombosis**. Thus, 30% MeNH2 soln. was added to a soln. of 2 g II (R3 = Me, R4 and R5 = H, Z = O, R = Ph) in MeOH and the mixt. let stand overnight room at temp. to give 0.8 g I (R1 = R4 = R5 = H, R2 = R3 = Me). Among ca. 17 more I similarly prepd. were (R1 = R5 given): H, Me2N-(CH2)2, H, H, H; .apprx.NR1R2 = 4-methyl-1-piperazinyl, H, H, H; H, Me2N(CH2)3, H, H, H; Me, Me, H, 6-Me, 7-Me.

IT **53629-35-9**
RL: RCT (Reactant)
(amidation of)

RN 53629-35-9 CAPLUS
CN Carbonic acid, (3,4-dihydro-4-methyl-3-oxo-2-quinoxalinyl)methyl phenyl ester (9CI) (CA INDEX NAME)



L5 ANSWER 60 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1974:463679 CAPLUS
DOCUMENT NUMBER: 81:63679
TITLE: Quinoxalines
INVENTOR(S): Inoue, Michiro; Ishikawa, Masayuki; Tsuchiya, Takashi; Shimamoto, Takio

09/ 773,374

SOURCE: Japan. Kokai, 7 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 49024983	A2	19740305	JP 1972-63688	19720627

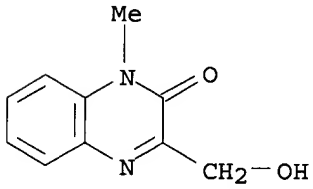
GI For diagram(s), see printed CA Issue.

AB 2-Hydroxymethyl-3-oxo-3,4-dihydroquinoxalines I (R3 = H or alkyl; R4 and R5 = H, halogen, alkyl, alkoxy, CO2-H, or alkoxycarbonyl) were treated with COCl2 and the resulting chlorocarbonates (II) treated with NHR1R2 (R1 = H or alkyl; R2 = H, alkyl, cycloalkyl, dialkylaminoalkyl, alkenyl, aryl, or aralkyl; NR1R2 may form a heterocyclic ring) to give the title compds. (III). III are remedies for arteriosclerosis and **thrombosis**. Thus, 5.5 g COCl2 in 50 ml PhMe was added to a cold (-5.degree.) mixt. of 9.2 g I (R3 = Me, R4 = R5 = H), 7 g PhNMe2, and 300 ml PhMe, the mixt. stirred 5 hr at 0-5.degree., and the resulting chlorocarbonate treated with 3.2 g MeNH2 to give 6.8 g III(R1 = R4 = R5 = H, R2 = R3 = Me). Among .apprx.17 more III similarly prepd. were the following (R1-R5 given): H, Me, H, H, H; H, Me2N(CH2)2, H, H, H; NR1R2 = 4-methylpiperazino, H, H, H; Me, Me, H, 6-Me, 7-Me.

IT **53378-13-5**
RL: RCT (Reactant)
(carbanoylation of)

RN 53378-13-5 CAPLUS

CN 2(1H)-Quinoxalinone, 3-(hydroxymethyl)-1-methyl- (9CI) (CA INDEX NAME)

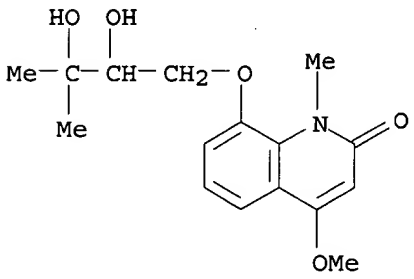


L5 ANSWER 61 OF 61 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1974:103870 CAPLUS
DOCUMENT NUMBER: 80:103870
TITLE: Comparative pharmacological study of the antiarrhythmic properties of foliosidine, quinidine, and novocainamide
AUTHOR(S): Polievtsev, N. P.; Azimov, M. M.
CORPORATE SOURCE: USSR
SOURCE: Farmakol. Alkaloidov Ikh Proizvod. (1972), 58-64.
Editor(s): Sultanov, M. B. "Fan": Tashkent, USSR.
CODEN: 27NBAD
DOCUMENT TYPE: Conference
LANGUAGE: Russian

AB Foliosidine (I) [**2520-38-9**], injected i.v. at 20-30 mg/kg into cats, prevented **cardiac** arrhythmia induced by CaCl2 or adrenaline. Its effect persisted for 20-60 min. The antiarrhythmic effects of novocainamide [51-06-9] or quinidine [56-54-2] at 10 mg/kg persisted only for 5-15 min. Quinidine at 20 mg/kg caused lethal decreases of the arterial pressure and respiration rate. Novocainamide at 20 mg/kg has also a significant hypotensive effect. The LD50 value of I, injected i.v. into mice, was 209 mg/kg.

IT **2520-38-9**

RL: BIOL (Biological study)
(heart arrhythmia response to)
RN 2520-38-9 CAPLUS
CN 2(1H)-Quinolinone, 8-(2,3-dihydroxy-3-methylbutoxy)-4-methoxy-1-methyl-
(9CI) (CA INDEX NAME)



=> d his

(FILE 'HOME' ENTERED AT 14:07:50 ON 01 APR 2002)

FILE 'REGISTRY' ENTERED AT 14:07:58 ON 01 APR 2002
L1 STRUCTURE UPLOADED
L2 50 S L1
L3 12751 S L1 FUL

FILE 'CAPLUS' ENTERED AT 14:08:56 ON 01 APR 2002
L4 2424 S L3
L5 61 S L4 AND (THROMBOSIS OR THROMBUS OR CARDIAC OR ANGINA OR INFARC

=> log y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	278.24	419.11

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-37.79	-37.79

STN INTERNATIONAL LOGOFF AT 14:12:32 ON 01 APR 2002